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Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices:
535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1,
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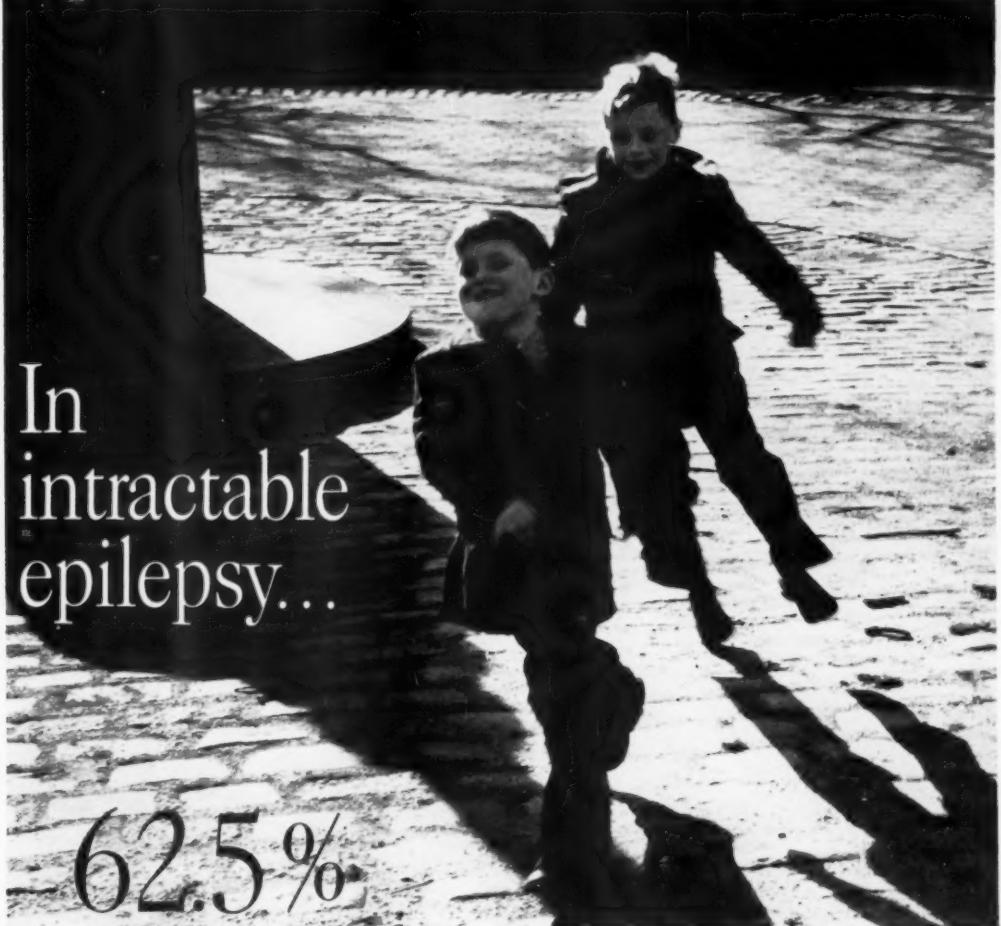
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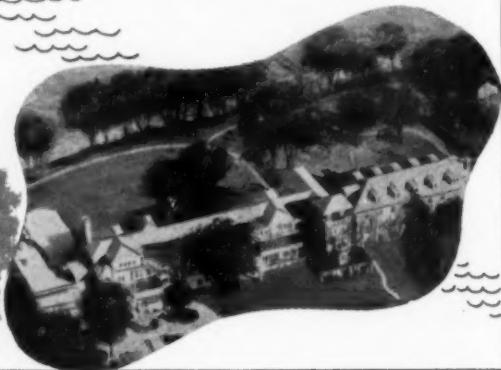
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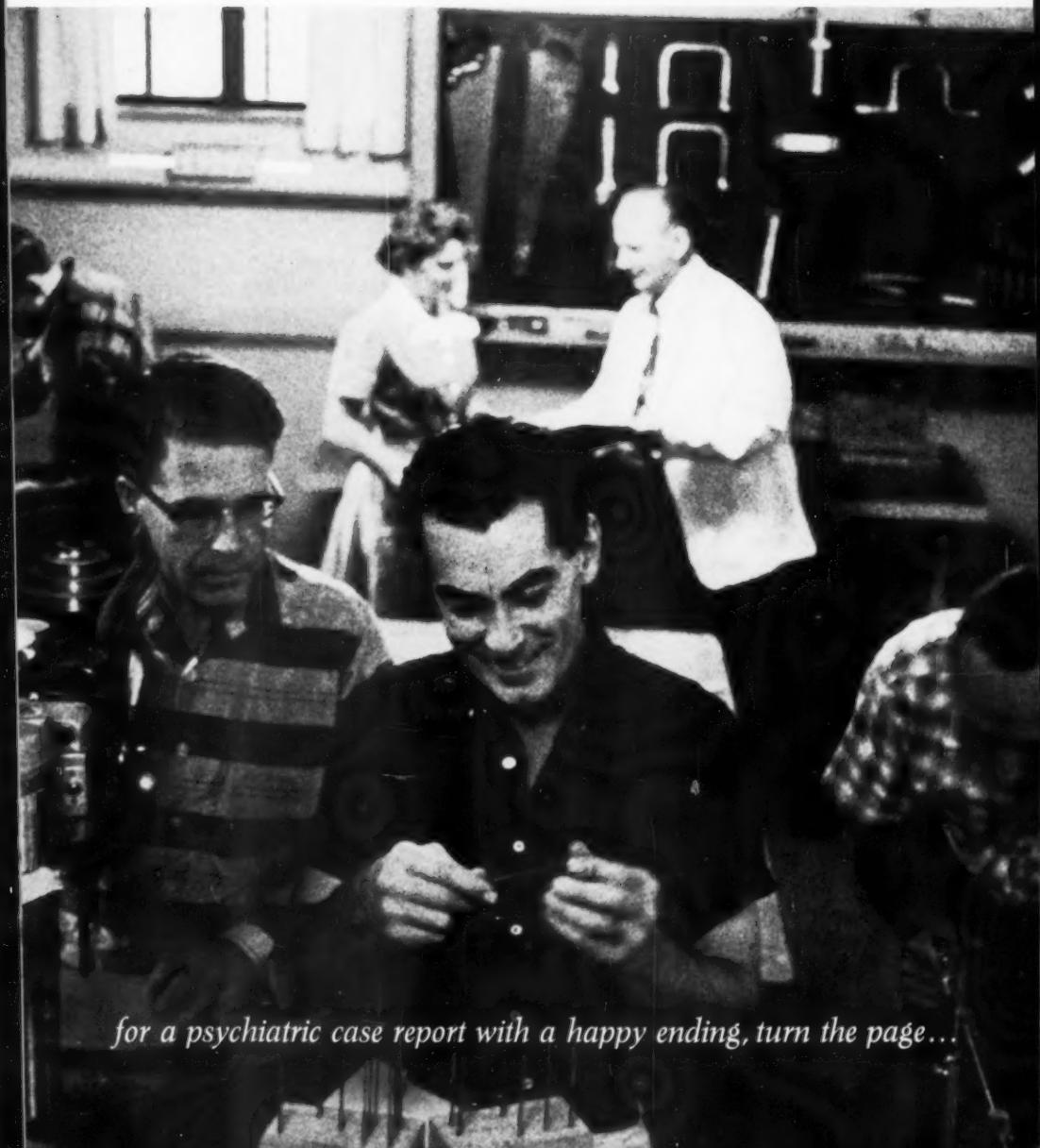
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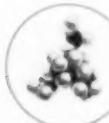
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NON-PARANOID	45	34	TENSION	31
DEPRESSION			AGITATION	8
PSYCHOTIC†	37	25	OTHERS	11
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SECTION ON
NEUROLOGY

Illusions of Comparative Interpretation and Emotion

Production by Epileptic Discharge and by Electrical Stimulation in the Temporal Cortex

SEAN MULLAN, M.D., and WILDER PENFIELD, M.D., Montreal

"We now consider," wrote Hughlings Jackson¹ in 1880, "certain psychical states during the onset of epileptic seizures which are much more elaborate than crude sensations."

"I speak first," he continued, "of certain highly elaborate mental states, sometimes called 'intellectual auras.' . . . The state is often like that occasionally experienced by healthy people as a feeling of 'reminiscence.' . . . It is sometimes called 'dreamy feelings' or is described as 'dreams mixing up with present thoughts,' 'double consciousness,' 'feeling of being somewhere else,' 'as if I went back to all that occurred in my childhood.' These are all voluminous mental states and yet of different kinds; no doubt they ought to be classified."

In recent years we have studied these "psychical states" clinically, as Jackson did. They may appear in the onset of an epileptic seizure that originates in temporal regions of the brain, and they may, in fact, constitute the only clinical manifestation of such an attack. We have also been able to produce them by electrical stimulation of the

temporal lobe of conscious patients, and with increased experience one of us (W. P.) has come gradually to the general classification that follows.²

A. Psychical hallucinations. These are produced by the recall of past experience in detail with all that fell within the patient's attention at the time. They are better called experiential seizures, or experiential responses to stimulation.

B. Psychical illusions. Here we have the misrepresentation or altered interpretation of present experience, better called illusions of comparative interpretation, or interpretive illusions.

C. Psychomotor automatism, a period of confused behavior with amnesia.*

In this study we are concerned with the second group—the *illusions of comparative interpretation*—as they have occurred spontaneously or as the result of cortical stimulation in 70 of a consecutive series of 214 patients treated surgically in recent years for relief of their temporal lobe seizures. This series was reviewed critically by S. M. We have also added three cases of a pre-

Accepted for publication March 20, 1958.

Read at the 81st Annual Meeting of the American Neurological Association at Atlantic City, June, 1957.

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* A staring expression with movements of mastication and swallowing is often the signal of the onset of this epileptic state. Whatever the stage of confusion, the patient invariably has subsequent amnesia for the period. His behavior has been likened to that of an automaton and the condition therefore called automatism. Consciousness is not completely lost, but the recording mechanism of present experience seems to be paralyzed.³

vious series because of their special interest.

An illusion may be defined as a faulty interpretation of present experience or present environment. During a psychical illusion, a subject's awareness is altered by some change that arises spontaneously within the brain. These psychical illusions are alterations in the subject's interpretation of his present state, his present environment, his present existence, and differ essentially from the hallucinations, which are an awareness not of the present but of a different or previous experience.

Illusions have to do with the intensity of the subject's interpretation of his environment, with a consideration of the relationship of the various units and factors of his environment to one another and to himself—particularly to himself—and with the manner in which the environment fits into his previous experience of things. Lastly, the illusions may have to do with his emotional state at the moment. Perhaps it might be held that a feeling or emotion occurring in a seizure is not an altered awareness but a new awareness; but insofar as they are interpretations of the present, they are illusional phenomena and not hallucinations.

It is of interest, too, that in few of these cases has any doubt been expressed of the essential meaning of things. Unlike psychotic persons, these patients were aware that the altered interpretation was an illusion. As will be described later, a friend's voice may sound remote, or a well-known living room may appear unfamiliar; but the meaning is preserved, the voice does not become depersonalized, nor does the living room lose its identity. Even those patients describing feelings of unreality state that they know at the same time what reality is, though it may be that the feeling is so short that the realization and rationalization are almost simultaneous. Only in occasional cases of intense fear did these patients seem to be unaware of the illusional nature of the experience.

Considering the relatively large number of examples of illusion, it seemed advisable to subdivide them into a useful classifica-

tion, as suggested by Hughlings Jackson. In the first attempt we placed the numerous illusions of change in sight and sound together and then divided them into apparent alterations in shape, size, distance, and intensity. That seemed to give us no corresponding differences in localization; in other words, there was no cortical area consistently associated with "bigness," or "nearness," or any such dimension. Next, we tried dividing the group simply into auditory illusions and visual illusions. With this second, simple classification there appeared clearly recognizable differences in cortical localization. This was taken as a reasonable justification, and so the classification was adopted, adding to these two groups the numerous illusions of familiarity and of fear.

Thus we ended with four major groups.

1. Auditory Illusions: Sounds seemed louder or clearer, fainter or more distinct, nearer or farther.
2. Visual Illusion: Things seemed clearer or blurred; nearer or farther; larger or smaller; fatter or thinner.
3. Illusions of Recognition: Present experience seemed familiar, strange, altered, or unreal.
4. Illusional Emotions: Feelings of fear, loneliness, sorrow, or disgust.

To this list we must add a few others less commonly encountered. They are illusions of increased awareness, illusions of alteration in speed of movement, and, lastly, visuovestibular disturbances, in which objects appear tilted to one side. Most could be regarded as variations of visual or auditory illusion, though the illusion of altered awareness did also embrace the sensations of smell and proprioception.

Materials and Methods

The location of those points whence illusions were elicited has been summarized on the accompanying maps (Figs. 1-5), and, though wide areas of the cerebral cortex were stimulated at these and at many other operations, it is interesting that only from the temporal lobe and the surface of the adjoining insula have these illusions been produced. In these maps the depth of stimulation in buried gray matter is indicated

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below the figure by a dash (1 cm.) or a dot (0.5 cm.), and where the depth is indefinite, a series of small dots is employed. In interpreting these diagrams, it is well to remember that the stimuli may have been effective not at the precise point of application but at a distance by conduction, for sometimes a wide area of abnormally functioning brain may produce, on stimulation, only one type of response, owing to facilitation or a lower threshold for that response.

Approximately half the 217 operations were on the left side and half on the right. Only 40% of patients, however, showed evidence of aphasia, either in association with their seizures or, more commonly, in the postoperative period, in association with local edema. In a few cases aphasia was produced while speech cortex was subject to stimulation. In all these patients (40%) it was clear that the operation had been carried out on the hemisphere dominant for speech. The disproportion between dominant and nondominant cases selected for operation arises from a reluctance to accept those cases in which any danger of permanent postoperative aphasia existed.

Of the patients, 20% were left-handed (normal is about 5%); some few were ambidextrous. The abnormally large number of left-handed persons is due to the fact that some of these patients had sustained birth injuries or other damage in early life, many of those affected on their left side becoming left-handed as a result.

The pathology encountered at these operations (except in a few cases of tumor or vascular abnormality) was a local atrophic process, similar to that described by Earle, Baldwin, and Penfield.⁴

Report of Cases

A few examples of the types of illusion encountered are presented. Except where otherwise mentioned, the left hemisphere was dominant for handedness and for speech. Unless specifically mentioned, aphasia was not recorded or produced. (Further reference to cases marked with the dagger in the text or in the legends

may be found in Penfield and Jasper² 1954.)

Visual Illusions of Perceptual Intensity (11 cases).—Eight cases of blurred vision have been encountered. In three the illusions were experienced at operation only. Two occurred both in the seizure and at operation.

CASE 4.—V. V., a man aged 28. This man's seizures commenced in early childhood. Illusion pattern: (1) abdominal aura, fright; (2) palpitation; (3) visual phenomena and psychical hallucinations; (4) kissing; (5) automatism. There was a tendency to macropsia, which was not well described. If reading, he said that words grew bigger and blurred. Operation: right. Stimulation: "A drawing feeling in my stomach, and something seems to be going across my eyes, like a vision in a fog." When asked if this were like his attack, he said "yes."

In three cases the impression of more distinct vision was a feature of the seizure but was not observed at operation.

CASE 10.—G. C., a woman, aged 27. This woman had a brief history of seizures. Physical examination suggested the presence of a tumor. Pattern: (1) sense of weakness; (2) smell; (3) familiarity; (4) visual illusions of slow movement, increased fixity of the immobile objects and increased visual detail (e. g., in one attack, looking at her hands, she observed that the skin pattern was extremely well defined); (5) tingling vaginal sensation. Operation: right temporal glioma.

In all cases, the illusion, whether of blurred or more distinct vision, was considered to arise in the nondominant temporal lobe.

Visual Illusions of Spatial Interpretation (12 cases).—In three cases the illusion that things seemed to be at a distance was encountered in the seizure pattern. At operation it was reproduced by stimulation in two cases and occurred in an additional two cases without having formed part of the clinical attack.

CASE 12.—B. J., a woman, aged 29, had had seizures since she was 18 years old. Pattern: (1) abdominal and cephalic aura, together with a feeling that things were at a distance; (2) stiffening sensation in the left hand and left side of the body; (3) occasional memory of something she had known in the past; (4) hyperpnea; (5) automatism. Operation: right. Stimulation: RJ (Fig. 1), 2 cm. deep. A short seizure was produced, and later the patient stated that she knew the attack was coming because, referring to two

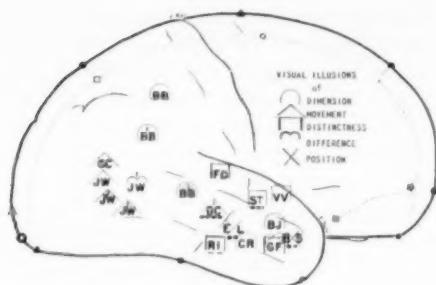


Fig. 1.—Map indicating sites where electrical stimulation produced visual illusions.
Case 1.†—*GF*: People seemed to get smaller and farther away.

GF, at 2 cm.: "Her dress [the nurse] was tight like a sheet." "That is what is hard to put into words . . . that is what I notice in my attacks."

Case 2.—*FD*: "As if I did not recognize you." "Something peculiar in the appearance of Dr. Pasquet."

Case 3.†—*ST*: Everything looked blurred—"a blinking."

Case 4.—*VV*: "Something seems to be going across my eyes like a vision in a fog."

Case 5.—*RI*: "A cloudy something before my eyes."

Case 10.—*GC*: Movement that Dr. Karagulla made with her hands appeared to slow down.
GC 1, 3 cm. deep: "Things are flickering."

GC 1, 4 cm. deep: "Everybody is stationary."

Case 12.—*BJ*: "You both looked more distant—you both moved that way."

Case 13.—*CR*: "Everything looked funny—and much farther away."

Case 14.†—*BB*: Things looked farther away, as in an attack.

BB 1: When asked whether things seemed farther away, she said "yes."

BB 2: "Things are going away"; she added that they all got smaller.

Case 28.†—*JW*: "Things looked different—just a trembling-like" sensation.

JW 1: Different—dark.

JW 2: "The start of an attack." "The way things are moving."

JW 3: "The same—the way things look."

Case 37.—*EL*: "Everything looks funny—things look as if they were sideways a little."

Case 41.—*BS*: She could not see straight and said the lines were out of kilter. "Like an attack, and not being able to see straight and falling over."

doctors who were present, "you both looked more distant." On repeated stimulation, she said, "You both moved that way."

The illusion of nearness was encountered in three cases but was not reproduced at operation. Largeness was encountered in four cases, while micropsia was a feature of the seizure in two instances and was encountered twice at operation. Illusions of objects being large and close occurred in the seizures of two, while to one patient objects appeared large and distant. At operation, this woman also observed them to be small and far away. There was one instance of distortion, in which seizure people and objects appeared tall and thin or low and fat.

In 8 of these 12 cases of visual illusion, the left hemisphere was dominant for handedness and speech, and in 1 case the right hemisphere was dominant for both. In these nine cases, the operation was on the minor

hemisphere. The sites of positive stimulation are found in Figure 1. In two cases the operation was on the left side, which was major for speech but was minor for handedness.

CASE 17.—H. Cu.,† a man, aged 45. Left hemisphere dominant for speech; right hemisphere dominant for handedness. Seizures for six years. Pattern: (1) macropsia and illusion of nearness; (2) respiratory arrest; (3) mastication; (4) automatism. Persons and objects were seen to grow large. On one occasion the cinematographic screen seemed to be coming very close. At the commencement of one attack, which was closely observed, he said: "Wait a minute; you are getting bigger. The nurse is standing beside you. She is getting bigger. Watch me!" Operation: left. Old adhesive lesion in the neighborhood of the insula. Aphasia present postoperatively.

In an additional case, the operation was also on the left side, which in this instance was major for both speech and handedness. This patient had marked bilateral brain damage.

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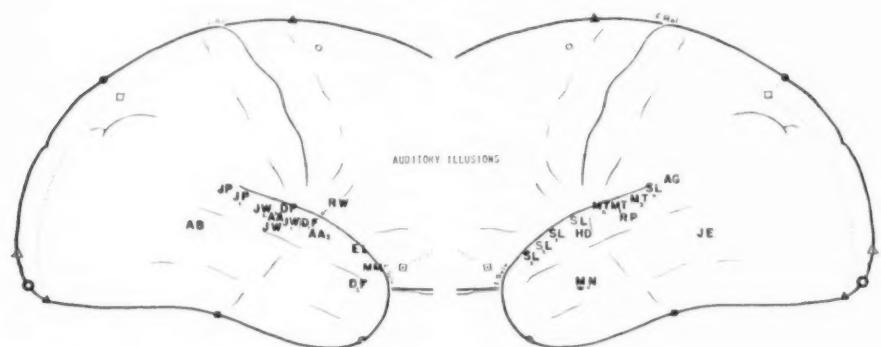
Auditory Illusions of Perceptual Intensity (11 cases).—Sounds were heard louder in five instances and better in one. In three cases the illusions arose in the major, and in three in the minor, hemisphere.

CASE 25.—S. L., a man, aged 35. He had many head injuries, being a football player and boxer. His attacks commenced at the age of 21. Pattern: (1) auditory illusion; (2) occasionally an olfactory sensation; (3) generalized convulsion. The auditory component of his attack took the form of a sudden buzzing in both ears or of a period of extreme stillness. He did not know whether he could hear at all at that time. He said there was a complete silence. The buzzing sound was "like a bee coming from a distance on each side." (He moved two fingers toward his ears and made a buzzing

sound in crescendo ending with a bang.) Operation: left. Stimulation: *SL* (Fig. 2); "Your voice is hard, like a roar." Aphasia was present.

Of the five cases in which sounds were less well heard, four were related to the minor, and one to the major, hemisphere. In two the illusion occurred in a seizure only and in eight at operation only, while in one it occurred in both.

CASE 30.—D. F., a woman, aged 26. Left hemisphere dominant for speech; patient almost ambidextrous, with a preference for her right hand. After arrest of respiration during an anesthesia at the age of 5 years, this patient frequently complained of substernal sensations, only recognized as seizures when convulsive movements developed in later years. Pattern: (1) thoracic sensation; (2)



- Fig. 2.—Map indicating sites where electrical stimulation produced auditory illusions.
 Case 23.—*MN*: "Oh, there is a difference in the sounds."
 Case 24.—*MM*: "Everything seemed very familiar. My own voice sounded louder."
 Case 25.—*SL*: "Your voice sounded as though you were shouting at me."
SL 2: "A noisy voice with a feeling of quiet all around."
SL 3: "A feeling of quiet all around my body."
SL 4: "Feeling that your voice is sharp, and as though I was punch drunk, you know, just going into a thing."
 Case 26.†—*AB*: "Now I can hear your voice better."
 Case 27.—*MT* 1: "Not quite so clear."
MT 2: "The sound of counting was not so clear."
MT 3: "Rather faint to hear."
 Case 28.†—*JW*: "Nothing except I hear differently." He said it was a kind of a deadener sound.
JW 1: The same effect.
JW 2: "It was as if I had something stuck in my ears right at that time."
 Case 30.†—*DF*: "It was as though your voice was blocked off."
DF 1: "My voice sounds funny to me."
DF 2: "My voice sounds funny."
 Case 31.†—*JP*: "I can't hear."
JP 1: "Deaf."
 Case 32.—*JE*: "I could not hear. You went further away."
 Case 34.—*ID*: All the sounds seemed to be distant.
 Case 35.†—*AA* 1: "It seems as though things are far away."
AA 2: "My left ear—sounds as though things are far away."
AA 3: "My right ear seemed to hear things far off."
 Case 36.—*AG*: "Things are distant." "My ears are plugged."
 Case 37.†—*EL*: "Everything sounds far away." "Your voice is far away."
EL 1, 1 cm. deep: "Things seem far away."
EL 2, 2 cm. deeper and more posteriorly: "Everything sounds far away."
 Case 38.—*RW*: "A feeling of sounds coming from a long distance."

mastication; (3) occasional major convulsion. Operation: right. Stimulation: *DF*. The operator began counting, and at the moment the stimulation was applied, the patient said: "It was as though your voice was blocked off." *DF 1*: "My voice sounds funny to me." *DF 2*: "My voice sounds funny."

The proximity of these responses (Fig. 2) to the primary auditory areas suggests that the reception of the primary sensations, rather than an interpretation, may have been affected. This applies particularly to those responses of diminished sensation.

Auditory Illusions of Spatial Interpretation (9 cases).—In the seizure history of three cases, sounds appeared to recede, and in one of these, and in five others, the illusion of receding sound was produced at operation.

CASE 34.—H. D., a youth, aged 16. At 11 years of age he fell upon a nail and sustained a penetrating wound of the left temporal region. A small bone defect was visible in his x-rays low down on the lateral wall of the left middle fossa. Pattern: feeling of unreality and familiarity. Operation: left. Stimulation: *HD* (Fig. 4). The patient felt queer; he elaborated by saying that, although he had never felt it before, all the sounds seemed to be distant. Aphasia: present.

Of these nine cases, the minor hemisphere was considered to be the site of the lesion in five; in two it was in the major hemisphere, and in one case dominance was mixed. In one case the illusion of approaching sound was produced.

CASE 16.—R. L., a woman, aged 26. Pattern: (1) Visual and auditory illusion. A sudden feeling came over her, an experience that objects seen seemed to come close to her and that things heard sounded louder and nearer. (2) Head turning to the left, with the appearance of fear and brief amnesia. Operation: right.

Illusions of Greater Awareness (2 cases).

This illusion was encountered in two cases (both related to the minor hemispheres) and was evoked at operation in one of them.

CASE 38.—R. W., a man, aged 25. Seizures since the age of 19. Pattern: (1) rising epigastric aura; (2) illusion of greater awareness; (3) unconsciousness; (4) mastication; (5) automatism. This illusion of greater awareness was applied to smells, sounds, visible objects, and pressures. He called it "new awareness," of, for example, the character of cigarette smoke, or the appearance of his back yard, which he could see as though in geometrical

outline. On one occasion the seizure commenced at the cinema; and, as he walked out, he was unusually conscious of the weight of his coat and of the weight of his feet upon the floor. Operation: right. Stimulation: *RW* 1 cm. deep. This produced a sensation in his right foot. He asked if it could be repeated because he felt, as he did in his attacks, an increased awareness.

Illusions of Position, or Visuovestibular Sensations of Altered Position (4 cases).—Such illusions occurred in the seizures of two patients, and at operation in two others. All were related to the minor hemisphere. One patient had also what appeared to be a proprioceptive illusion of size, a Coca-Cola bottle in his hand feeling as large as a baseball bat.

CASE 41.—B. S., a woman, aged 35. Right hemisphere dominant for speech. Patient writes with her left hand but does heavy work—for example, sawing with her right hand. Her father is said to be ambidextrous. She had a head injury at the age of 5 or 6 months. Seizures commenced at the age of 3 years. Pattern: (1) fear; (2) cry; (3) sometimes salivation; (4) automatism; (5) dreams. Operation: left. Stimulation: *BS*, posteriorly (Fig. 5): "There was a vibration in my head." *BS*, 2 cm. straight in: She said she could not see straight and explained afterward that the lines were "out of kilter." During slow introduction of the stimulating electrode, she said: "Like an attack and not being able to see straight and falling over." Aphasia: none.

Illusions of Alteration in Tempo and in Movement (3 cases).—A visual illusion that the speed of moving persons or objects slowed down occurred in the seizure pattern of one patient and was reproduced at operation on her minor temporal lobe (Case 10; *GC*, already referred to under "Visual Illusions of Perceptual Intensity"). If she was looking at moving things or persons, it appeared as though the movements had slowed down, were extremely well defined and conspicuous, and almost composed into their different parts. She compared the illusion to "a movie going slow motion." During the seizures she had the impression that her own movements were slowed down, too, although her husband said they were not. If she was looking at an immobile object, it appeared as though it were "still more fixed." Her surroundings seemed to be at "double standstill." Objects far away

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appeared to her on occasions as though she were looking through the wrong end of a telescope. Operation: right temporal glioma. Stimulation: GC: "Standstill." It appeared to her that movements Dr. Karagulla made with her hands had slowed down. GC 1 (Fig. 1): 3 cm., straight in: "Oh, here we go again; things are flickering; the curtains on the left are stationary." Again, 4 cm. in, a little more anteriorly: "Oh, the smell! Everybody is stationary." GC 2, behind and below point GC: black and white lights flickering before her eyes. (A somewhat similar flickering experience occurred in another case of stimulation at approximately

this same area.) The sites of stimulation in Case 10 (GC) are seen in Figure 1.

An auditory illusion of increasing speed was encountered on one occasion and was thought to arise from a minor temporal lobe.

CASE 22.—W. Sh., a man, aged 30. Pattern: (1) thoracic sensation; (2) auditory illusion; (3) thoughts or words in his mind; (4) inability to understand words; (5) face movement to the right; (6) automatism; (7) probable aphasia. In the change in sound, he thinks that when he is listening to a continuous sound, it becomes louder. In addition, when he is working around a machinery plant, the machinery sounds faster. Operation: right.

Illusions of Familiarity (10 cases).—These formed part of the seizures of 10 patients and were reproduced in 6. In nine,

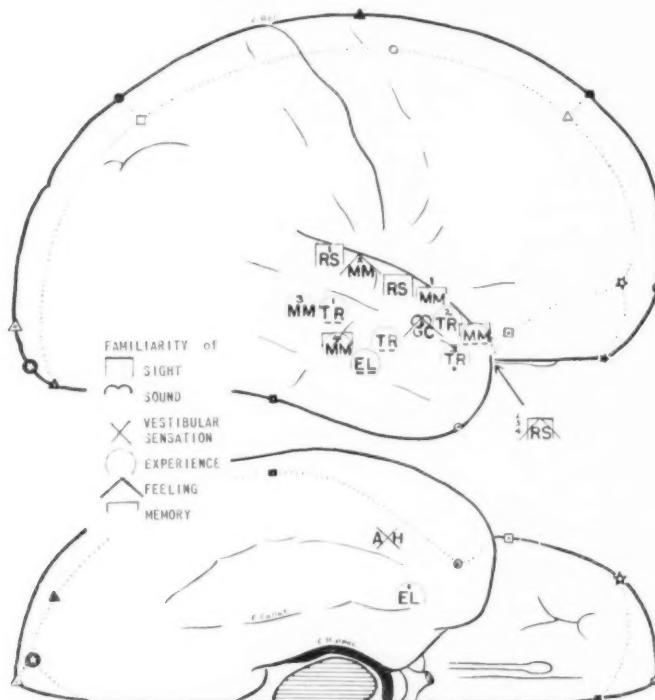


Fig. 3.—Map indicating sites where electrical stimulation produced illusions of familiarity.
 Case 10.—GC 3: The operator's voice seemed familiar. "As if I had heard you before many years ago in another place." Repeated. The same familiar quality. "It began before you spoke." The stimulation was actually begun before the operator said "now."
 Case 24.—MM: See text.
 Case 43†—EL, 2 cm. deep: "As though I had been through this before."
 Case 43†—EL 1: He had a feeling such as he experienced in his attacks—a feeling of familiarity.
 Case 45.—RS: "Things seem familiar," and he added that they looked vivid.
 Case 46.—AH: "I had a feeling as though I were standing up and falling over toward the floor." It was a familiar feeling, as though the patient had done it before, though he knew he had not.

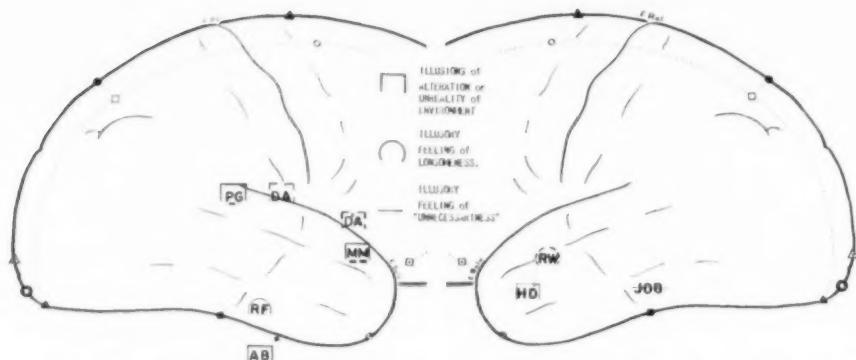


Fig. 4.—Map indicating sites where electrical stimulation produced illusions of unreality, of lonesomeness, and of unnecessariness.

Case 24.—MM:—"There was a feeling as though I were somewhere else, as though you were all waiting here for me to come back. I have had that feeling before."

Case 26.—AB: "I just seemed to lose control of my thoughts. Whatever I am visualizing just seemed to go away, and seems unusual."

Case 49.—HD: "As if I were not here."

Case 51.—JOB: "Strange feeling like it is unnecessary—the craziest, doggone feeling."

Case 54.—DA and DA 1 (both points are on the insula): "Out of this world."

Case 55.—PG: "Very frightened—I was not in this world."

Case 64.†—RW: Insula: Lonesome scared feeling.

Case 71.—RF: The all-alone feeling, "just like I do before an attack."

illusions were considered to arise in the right, nondominant hemisphere. The distribution of positive stimulation responses is shown in Figure 3. In seven cases the illusion referred to the experience or environment at the time. In three of these the response was regarded as particularly visual, while in one it was predominantly auditory. In one it was both auditory and visual. The following case is an example of the type most commonly encountered.

CASE 44.—T. R., a youth, aged 16. Pattern: (1) gustatory sensation, a bad taste which he likened to poor ginger ale; (2) illusion of familiarity; (3) automatism. This boy has had illusions of familiarity since early childhood, a feeling of "repetition" of circumstances. He could recall playing with his brother and feeling that the whole thing had happened before. At the age of 11 his doctor made a note of his saying: "Mother, I feel very queer, as if I had lived this part of my life before." During the year before admission he had three major seizures, each precipitated by hyperventilation. Operation: right. A racemose hemangioma was discovered on the undersurface of the temporal lobe. Stimulation: TR, 2 cm, deep in the anterior temporal region. The patient said "Ah," and then: "I just got the taste that I get before my attack." Stimulation was continued and then withdrawn. After withdrawal, he said: "I

had the feeling of repetition, too." When asked to explain, he said: "It is a feeling that comes over me, as though the whole set-up had occurred before." TR 1, depth of 2 cm, slightly more posteriorly: When the current was switched on, the patient said: "Nothing, except that I have that queer taste." After a brief period, he added: "And the feeling of repetition, all of the circumstances." TR 2: At this point, the patient got the feeling both of taste and of repetition. TR 3: He experienced only the feeling of repetition.

In one case the illusion at operation was referred not only to the environment of the moment but also to simultaneously evoked memories or hallucinations, so that they, too, took on the quality of familiarity.

CASE 24.—M. M., a woman, aged 26. Pattern: (1) illusion of familiarity; (2) psychical hallucination; (3) stiffening; (4) automatic behavior with salivation; (5) postictal amnesia. Her feeling of familiarity was described as "a feeling that I had lived through it all before." Operation: right. Stimulation: MM 1: "I heard something familiar; I do not know what it was." Later she explained that this was a sound of a mother calling her little boy, which she had heard many years before. MM 2: "A familiar feeling, very intense; I do not know what it was." MM 3: "I have a pain in my right eye, and the whole operation now seems familiar." MM 6.4 (the exact site is not indicated on the map): "Just a tiny flash of familiarity

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and a feeling that I knew everything that was going to happen in the near future. . . . As though I had been through all this before, and I thought I knew exactly what you were going to do next." MM, at a depth of 1 cm.: "Oh, I had this same very, very familiar memory in an office somewhere. I could see the desks. I was there, and someone was calling to me, a man leaning on a desk with a pencil in his hand." MM 4: "A familiar feeling; I know exactly what you are going to do." MM 4, stimulating near the uncus: "I have a very familiar memory of a girl talking to me." MM 5: "Familiar memory, the place where I hang my coat up where I go to work."

Illusions of Strangeness, Change, and Unreality (10 cases).—There were two instances in which the patient was aware of the exact opposite of familiarity, viz., of strangeness, and in both cases this feeling was applied to the immediate environment at the time of the seizure. The description given in each case relates to the visual recognition of that environment. Neither illusion was reproduced at operation. The disturbance in one of these cases was considered to arise in the minor hemisphere. In the other the site was doubtful, but was probably in the major hemisphere.

In another case (minor hemisphere) the environment was regarded as unusual, and in another (major hemisphere) it was described as being changed.

CASE 50.—D. C., a woman, aged 41. This woman's seizure history began at the age of 7, when she had a series of generalized attacks, lasting all night. Pattern: (1) abdominal aura, intestinal peristalsis; (2) illusion of strangeness; (3) confusion; (4) automatism; (5) postictal anorexia. On one occasion she described her illusion of strangeness as follows (she was in her living room at the time): "The living room did not look right. It looked strange. It just didn't look like my living room, and then it gradually came to look like mine." Operation: left. Aphasia: present.

In five cases (all but one were in the minor hemisphere) the relationship between the person and his environment was so altered as to be unreal. These patients did not refer to it as a subjective sensation of unreality, but in each the sensation of concrete reality with which we are bound to our environment was impaired.

CASE 56.—P. B.,† a man, aged 41. The patient had had a depressed fracture of the skull 16 years

previously. Pattern: (1) psychical illusion; (2) automatism. He described this illusion, which was not invariably present as a "queer feeling, as though everything were out of this world—the world is unreal; there is a strange feeling as though you weren't the same person you were before—there are waves of peculiarity in things." He also spoke of a feeling of absurdness or strangeness in things. Operation: left. Aphasia: present.

In one patient there was a consciousness of unreality related not to the total environment but to a particular object upon which attention was focused.

CASE 57.—W. W., a man, aged 42. Nine years before admission the patient had been involved in an airplane crash. Since then he had developed two types of attacks. In the first he seemed confused, speaking a little louder than normally, and frequently irrelevantly. In the other type he had what he described as a detached feeling. Pattern: He appeared pale and perspired at these times. Although he understood the nature of things, he had a feeling that they were unreal. As an example, he stated that if he had an attack he recognized that the x-ray-viewing box (which he could see at the time) was the x-ray-viewing box, but, at the same time, he might think to himself that he could put his hand through it. He used the word "unreal," but qualified it carefully to indicate that he knew what the actuality was. He remarked at the same time that if he was reading, he knew that the words in the sentence should make sense, but they did not. On occasions there were automatic movements and fairly prolonged periods of amnesia. Operation: left. Aphasia: present.

Illusions of Fear (23 cases).—Of the 217 cases under consideration, fear occurred in some form in 23. Seven patients were male. In two, it was associated with a fear-provoking hallucination, though in one of these it remained and was reproduced by stimulation subsequent to termination of the hallucinatory element of the seizure by operation.

CASE 58.—J. V.,† a woman, aged 32. It appears that at the age of 7, when she was walking through a field of grass, she was frightened by a man who came up behind her and asked her if she would like to get into the bag of snakes which he had and be carried away. Her seizures commenced at the age of 10. Pattern: (1) visual hallucination; (2) illusion of fear; (3) usually a short automatism, sometimes a generalized convulsion, beginning in the left side of the face and left arm. In these attacks she saw herself as a little girl walking across a field. Suddenly she felt as though someone from behind was going to smother her or hit

her on the head, and she felt frightened all over. She screamed out, calling her mother to hold "tight, tight, tight." Operation: Right occipital removal was carried out. Stimulation: JV: "Oh, there it goes; everybody is yelling. Something dreadful is going to happen." This was, however, different from her attacks. JV 1: "There they go yelling at me; stop them." JV 2: "I saw someone coming toward me, as though he was going to hit me. Don't leave me." Subsequent history: After this operation, this particular aura disappeared, but seizures with fear continued. Pattern: (1) awareness of fear; (2) scream, lasting 10 to 15 seconds; (3) automatic movements. She herself was unaware of any scream. Subsequent operation: right temporal. Stimulation: JV 3: "I had that terrible fear." Repeated, "Fear. Fear of an attack." JV 4, 4 cm. deep: Patient gave an exclamation and explained that there had been a strange feeling all over. "It started with a fear." JV 4, more anteriorly, 4 cm. deep: "A feeling above right eyebrow. ... They all started with a fear." JV 4, tip of electrode more posteriorly: "My chin quivered; this also started with a fear." JV 5, 2 cm. deep: She seemed disturbed, wept, was terribly afraid, and looked afraid.

In four patients the illusion had, possibly, other psychical associations, such as fear of death or insanity. These two groups of patients seemed to experience fear of an intensity much greater than that encountered in the others, as though a different quality of sensation was involved.

CASE 59.—C. B., a woman, aged 37. Her earlier attacks, which began at the age of 16, did not include fear. Later, fear formed a very prominent part, and after an attack she could remember it distinctly. Still later, although the attack pattern remained unaltered to the observer, the memory of the fear that was portrayed was lost. Pattern: (1) somatic sensation; (2) fear; (3) automatism; (4) sometimes convulsive movements of the left side of the body. She became very excited in her attacks, prayed, and clung to her husband with every evidence of terror; she was very much afraid of dying during those times, and talked about having people look after her children. Operation: right.

Four patients described a sensation of a fright, localized in one case to the sternum and in another to the "tummy"; in another there were pronounced borborygmi, while in a fourth the sensation was not localized.

Three described the sensation as a scared feeling, in one localized in the abdomen, in one associated with chills but without a sen-

sation of cold, and in one followed shortly after a general body sensation of warmth.

CASE 60.—N. K.,† a girl, aged 16. The patient was right-handed. Evidence of speech dominance was not conclusive, but the left hemisphere was thought to be dominant. Seizures commenced before she was 2 years old. Pattern: (1) fright and scream; (2) borborygmi and auditory sensation; (3) automatism. She was aware of a sudden fright, as though someone were standing behind her "exploding a balloon." She did not, however, hear any noise. She then felt a gurgling in her stomach and heard buzzing in her ears. Operation: left. Stimulation: NK (Fig. 5), on the anterior portion of the insula: "Yes, like an attack, a pang of fear." This was again produced on several stimulations of the same spot. Aphasia: none.

In two patients, the illusion was described as nervousness, in one as a nervous sensation in the stomach, and in another, as nervousness associated with a sensation of a knife being inserted into her back. In one patient there was a sudden sensation of terror on stimulation, but in five the fear was without other description, localized in two instances to the abdomen, and in two others fairly closely associated with pre-cardial and abdominal sensations, respectively. In two there was no appreciation of fear, but the appearance and behavior during the seizure suggested to the observer that the patient had experienced, but did not remember, an intense fear.

CASE 70.—A. L., a woman, aged 31. The patient's attacks commenced at the age of 6½ years. Pattern: (1) thoracic aura; (2) sensation of failing consciousness; (3) terrified shriek, tonic stiffening of left arm and leg, twitching of right side of face, and salivation; (4) automatism and mastication; (5) aphasia and confusion. Although she was not conscious of any fear, her terrified shriek and facial expression of terror led one to believe that the mechanism of fear was activated, though not recorded in her memory. Her mother likened her appearance to that of a person in the movies who comes into a dark room and finds someone there. Operation: left. Aphasia: present.

The appearance of fear, as already mentioned, was particularly obvious in the first groups. Of the total number there were vocalization in eight, a shriek in two, a scream in four, and a wavering cry in one; two patients wept. The sites in which the

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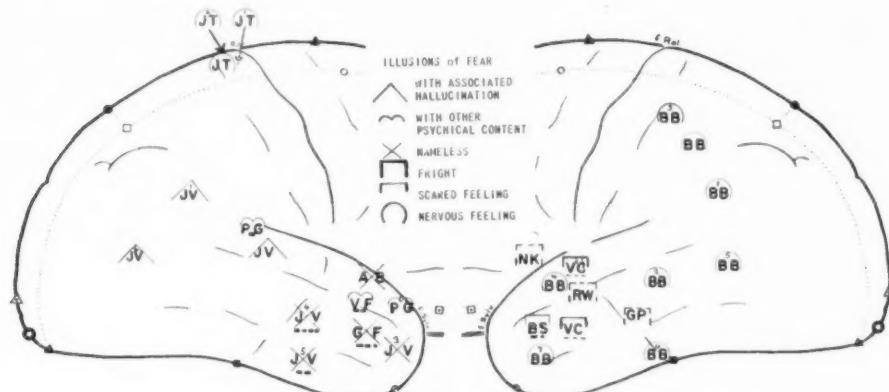


Fig. 5.—Map indicating sites where electrical stimulation produces illusional fear and nervousness.

- Case 14†—GF, 2.5 cm. deep: "That fear."
- Case 14‡—BB; BB 1; BB 3; BB 4; BB 7: "I feel nervous."
- BB 2: "Things are going away—and I am still nervous. I am afraid."
- BB 5: Stimulated without a previous warning. "The nervousness . . . like a knife sticking in my back."
- BB 6: Nervousness and a sensation in the back.
- Case 41—BS, 0.5 cm.: "Like the feeling before an attack, stronger than most of them." "This is not a feeling of fear because I am going to have an attack. It is a feeling of fear which is independent of myself."
- Case 48—I.F, 2 cm. deep: "Oh God! I am leaving my body." Patient looked terrified and made a gesture as though looking for help. Later he said: "I had the fear feeling."
- Case 52—AB: "I just felt terrified for an instant."
- Case 55—PG and PG 1: "Very frightened." He looked agitated and later explained that he was scared and was afraid he was going to die.
- Case 60‡—NK: "Like an attack. A feeling of fear."
- Case 61—GP: A feeling of fright.
- Case 63—VC; VC 1; VC 1, at 3-4 cm. depth: She felt scared all over, as in her attacks.
- Case 64‡—RW: A lonesome, scared feeling, as in his attacks.
- Case 65—JT; JT 1, and JT 2: "A kind of nervousness."

illusions were produced at operation are plotted in Figure 5.

Other Illusional Emotions (6 cases).—There were three cases of the emotion of loneliness. In one patient the feeling was elicited by stimulation of the left insula, and, although he did not have a well-defined postoperative aphasia, the left was probably his dominant hemisphere. In the other two, the lesion was considered to be in the dominant hemisphere. The illusion was reproduced by stimulation in two cases (Fig. 4).

CASE 3.—S. T.,† a girl, aged 17. Pattern: feeling of being all alone. These seizures began at the age of 15 months, and in the early ones she ran to her mother and clung to her knee. Later she described the sensation as that of being all alone and far away from people and of feeling that no one cared for her. Operation: right. A small calcified nodule, together with a cyst, were found at the anterior end of the temporal horn.

Illusory sensations of sorrowfulness appeared in the seizure pattern of one patient, and of absurdness in another. Another patient (P. B., already referred to) had feelings of disgust or unnecessariness, which were reproduced from the lateral surface of the major temporal lobe.

Comment

Visual and Auditory Illusions.—Distance is a dimension that can be estimated by sight, sound, and occasionally by touch, or by a combination of these. Since it is usually taught that spatial orientation is a function of the minor hemisphere, probably controlled by the parietal lobe, it would not have been surprising if the illusional estimation of spatial relationships, both visual and auditory, had been localized on the minor

temporal lobe. This, however, is apparently not the case. The auditory illusions were bilateral; the visual illusions were unilateral on the minor hemisphere. Not alone were the visual illusions of dimension represented on the minor hemisphere (except possibly in one case) but so also were visual illusions of perceptual intensity, visual-vestibular illusions, and visual illusions of speed. We, therefore, looked through previous records for evidence of any visual illusions arising in the dominant hemisphere, and there were two instances of these; but, interestingly enough, though both patients had temporary aphasia following that temporal lobe operation, both were left-handed, so that in these, too, the visual illusions were confined to the hemisphere which was nondominant for handedness. A search through the literature was less satisfactory, for in few instances were handedness and speech localization recorded. Nevertheless, there is in the literature, too, an impression that the majority of cases of visual illusions have had their etiological lesion in the nondominant hemisphere. Lund⁵ reported two cases; Gowers,⁶ Wilson,⁷ and Bender and Kanzer,⁸ each reported one case of visual illusions arising in the right hemisphere. Horrax,⁹ on the other hand, reported the occurrence of macropsia in a patient with a left temporal lobe tumor but did not definitely record handedness or speech localization. This lateralization of the visual illusions in the nondominant hemisphere is also in agreement with psychometric studies of Milner¹⁰ and Halstead,¹¹ both of whom found evidence of impaired eye-hand coordination in cases of lesions in the nondominant temporal lobe.

Of these, perhaps "blurred vision" should be regarded not as a true illusion but as a nonspecific result of a crude stimulus, but the fact that it is not limited to one-half the visual field suggests that it is something more than an interference with the optic radiation. It could also be regarded as a derangement of a power of accommodation, but its association with two possible cases of macropsia and with one visual-vestibular response suggests that in some instances it

may be a manifestation of derangement of the function of visual analysis, possibly related to the function of awareness, more clearly recognized, for example, in Case 38 (R. W.). There is a definite faculty by which we fix our attention upon a sight, sound, situation, or thought to the exclusion of all other perceptions or thoughts, a faculty which we call "concentration," or "attention." It is the faculty by which a golfer may keep his eye on the ball in flight, by which one can carry on a conversation against a background of incessant radio—a faculty which we bring to every phase of our appreciative and constructive activity. Those cases in which objects are seen more clearly or heard more distinctly, together with those of increased general awareness, suggest that a temporal lobe may play some part in this function of concentration. (The reverse of this—distractibility—has been noted in animals and in humans in whom there has been marked bilateral temporal lobe destruction.)^{12,13}

Familiarity.—The sensations of familiarity and of strangeness are constantly experienced in our every activity. Every object encountered is subjected to this analysis, whether it is known or unknown; yet so unobtrusive is the faculty that, unlike the emotions, we are scarcely aware of its existence. The intensity of its occurrence and the relative frequency of its incidence on stimulation are noteworthy. Though in the majority of these patients the feeling was related to a particular object or situation, in two cases it seemed to appear independently as a "pure," unattached sensation, e.g., in Patient M. M., who had an intense feeling which she could describe only in terms of familiarity. With Patient G. C., to whom the operator's voice was described as being familiar, the feeling of familiarity had already commenced before he spoke, as though the stage or background had been set to embrace in familiarity any dominant perception. In two cases, simultaneously evoked responses, experiential and illusional, were also included in the background. Patient M. M., who at operation heard a mother

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call her little boy—something she had heard many years before—considered that this hallucination was a very familiar one. Patient A. H., who on stimulation of his temporal lobe had a sensation of falling over—something which, in fact, he had not previously experienced—felt for the moment that the sensation was familiar.

Unlike auditory illusions, these feelings of familiarity did not occur without having

been present in the seizure, a feature which suggests that considerable "conditioning" in the abnormal temporal lobe was necessary for production of these feelings. The reference to Figure 3 shows that they were found over a fairly wide area, and this was true even in a single subject, indicating, perhaps, that the function of estimation of familiarity has a diffuse representation throughout the temporal lobe.

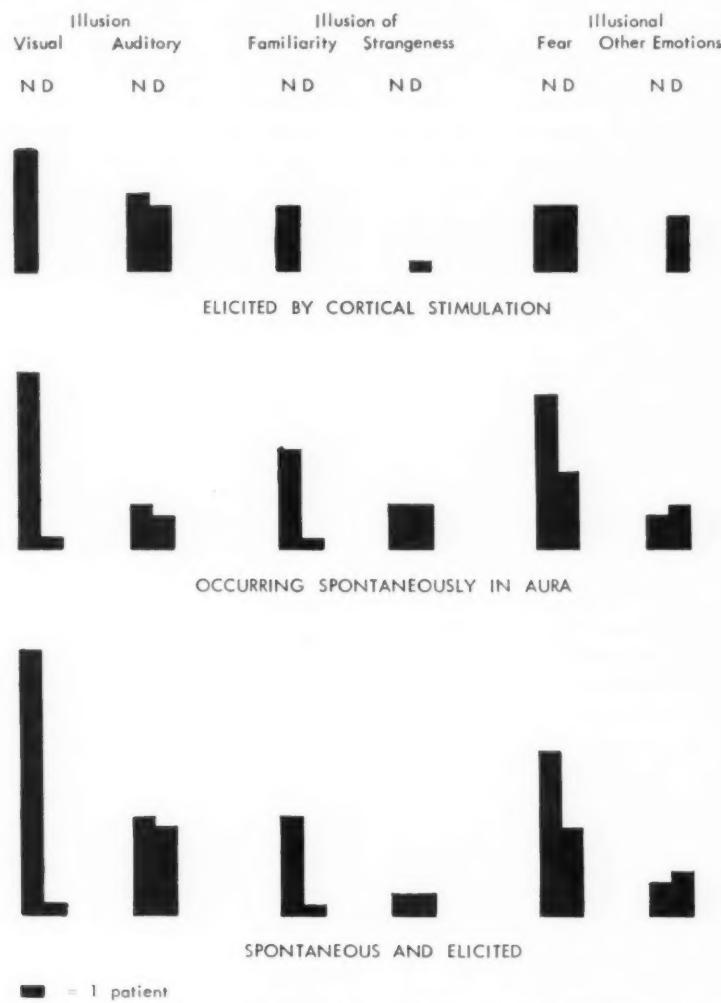


Fig. 6.—Lateralization of illusions. *N* indicates nondominant hemisphere; *D*, dominant hemisphere.

Sixty per cent of operations were on the nondominant hemisphere (*N*); 40% of operations were on the dominant hemisphere (*D*).

As with visual illusions, there is in this group a preponderance of minor-hemisphere cases, but the difference is less marked and the ratio is 9:1, rather than 22:1 (Fig. 6). It would, in addition, seem reasonable to consider familiarity and strangeness and change together as a group, in which case the proportions are reduced to 11:3. (It should be remembered that in this total series of approximately 200 patients the proportion of nondominant to dominant cases is 3:2.)

Emotional Fear.—A patient is rarely frightened of a seizure, but fear in a different sense, as an intrinsic part of a seizure, is relatively common, and occurred in 23 instances of the series. The distinction between fear of an attack and this fear in an attack was very clearly stated by Patient B. S. (Case 41), who said on stimulation of a point 1 cm. deep near the tip of her left temporal lobe: "This is not a feeling of fear because I am going to have an attack; it is a feeling of fear which is independent of myself." The intensity of fear varied widely from mild fright to sheer terror. There was no relationship between the intensities of the fear and the strength of stimulation or between the type of fear and the site of stimulation. The high incidence of abdominal, thoracic, or other bodily sensations accompanying the less intense manifestations of fear does not necessarily favor a localization adjoining known centers of visceral activity. Such sensations could be part of the physiological response. The close relation and sequence of fear and automatism is seen in the pattern of most of these seizures.

Apart from the cases of nervousness and fear which probably resulted from hallucinations it is seen from a study of Figure 5 that the emotion on stimulation was obtained almost entirely from the anterior half of the temporal lobe bilaterally. Of the 14 recorded responses, 11 were elicited from gray matter that could be reached only by deep stimulation. It should be remembered that, while superficial stimulation covered the whole operative field thoroughly, the deep electrode

was introduced in a few isolated points only. This pattern would, therefore, suggest that there is deep in the anterior part of the temporal lobe, probably related to the anterior medial surface, a neuronal mechanism intimately connected with the phenomenon of fear.

Rage we have never encountered. That patients with temporal lobe seizures are occasionally subject to uncontrolled anger is well known, but we have not encountered this as an aura of temporal lobe seizures, and we have not produced it by stimulation in the temporal area.[‡] Fear may be considered an interpretation of the present experience, like familiarity. Therefore it is not surprising to find it appearing in association with the other forms of interpretation of the present by comparison with the past.

Feelings of lonesomeness and sorrow, absurdity and disgust, were all encountered. The feeling of being "out of this world" might also be considered an emotional response.[§] It is remarkable that there was only one example of a pleasant sensation in the entire series. The number of these assorted emotions is too small to allow a localization more exact than the wide temporal cortex with which we are dealing.

Conclusion

The cortical area from which these illusions have been elicited is one of the old classical association areas—an area of no known function. Yet these illusions are but alterations of function made use of in everyday existence. The visual and auditory judgments of position and dimension, of tempo and direction of movement, are elements involved in the present perception of the environment. The feeling of familiarity is a signal of recognition, in total or in part, of present perception and experience. Fear

[‡] Behavior suggesting rage was produced in Patient M. R. (Penfield and Erickson¹⁴). The stimulation point was in the superior intermediate frontal region.

[§] An emotion is a "mental 'feeling' or 'affection'—as distinguished from cognitive or volitional states of consciousness."¹⁵

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is a signal that rises into consciousness as a result of an interpretation of what the present situation may bring to the subject in the immediate future, and is as much an interpretation of the present as is familiarity.

Present experience is never twice the same, but these recurring interpretations of that experience are the same from time to time and from case to case, as though they were standardized. If a patient has an illusion of micropsia, then this impression of smallness is repeated, whatever the nature of the object viewed. If the illusion is one of familiarity, then the sensation is the same whether he finds himself in his own home or under the arc lights of a neurosurgical operating room. A sense of dread or fear or sorrow is likewise an interpretation of the present and is the same, however varied the environment.

In normal life these are the signals that rise into consciousness, signals that depend upon subconscious comparison of past experience with the present. Since these signals, experienced before, bringing danger, coming near, going away, slowing down, can be produced by localized discharge of the temporal cortex, and not elsewhere, and since electrical stimulation may elicit them in that area of the cortex only, it is fair to conclude that they are produced by activation of separate, well-defined neuronal mechanisms.

Each of these mechanisms is in a sense a "final common path"; and when impulses flow along this path into the central integrating circuits, the subject is conscious of nearness, of familiarity, or of fear. During normal life he becomes aware of such signals after comparison of the present situation with selected strips from the past stream of consciousness. He becomes aware of the signal before he has time for volitional consideration. The comparison is made subconsciously. That being the case, it is not surprising to discover that the interpretive illusions are topographically related to the psychical hallucinations or experiential responses which are the recall of strips of past experience.

Summary

Illusions were encountered, either in the seizure pattern or as a result of stimulation at operation, in 70 of a series of 214 cases of temporal lobe epilepsy recently reviewed.

Lateralization of the origin of these illusions was arrived at by preoperative study. Further localization was made possible by operative exploration.

Maps have been constructed to summarize the location of the points of stimulation that produced the various forms of interpretive illusion.

Our conclusion is that visual illusions arise predominantly from the temporal cortex of the hemisphere that is minor for handedness.

Illusions of familiarity were predominantly associated with epileptic discharge or electrical stimulation in the temporal region of the hemisphere that is minor for handedness and speech. However, this preponderance is less invariable than in the case of the visual illusions.

Auditory illusions and illusions of fear were considered to arise in the temporal lobe of either hemisphere.

The greatest concentration of positive stimulation responses for the illusion of fear was in the anterior part of either temporal lobe, situated deep and medial.

In contrast with sensory and motor areas of the cerebral cortex, the temporal cortex (exclusive of the auditory area) is largely devoted to comparative interpretation of present perceptions. Somehow, it seems to analyze the components of sensation, compares them with previous experience, and, by that analysis and comparison, transmits into consciousness their present and immediate significance. It would seem that in the temporal cortex a limited number of interpretive signals can be produced, as though they are anatomical "final common paths" leading from the cortex to neuronal circuits and are intimately related to consciousness.

The University of Chicago (Dr. Mullan).

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Newcastle Disease Encephalomyelitis in Cats

II. Physiological Studies on Rhythmic Myoclonus

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The term myoclonus is used clinically to describe a wide variety of suddenly appearing involuntary movements or jerks not otherwise readily classified.¹⁻¹⁸ These myoclonic movements may be generalized, segmental, or even limited to one muscle or muscle group. They vary in force and complexity from mere muscular twitches to coordinated movements sufficiently violent to displace one or more limbs, or throw the subject to the ground. They may be isolated, intermittent, and of short duration, as in the myoclonus accompanying certain epileptic states. On the other hand, they may continue repetitively over prolonged periods of time. The movements, when widespread, frequently appear synchronously throughout many parts of the body, or present first in one region before bursting forth successively in others. In some instances the explosive outbursts seem to follow a definite rhythm; in others they are rather irregular in time. It seems evident, therefore, that clinical patterns implied by the word myoclonus differ tremendously, with the sole common denominator of rapidly appearing, involuntary contractions of skeletal muscle. For purposes of the present communication, the term will refer to seg-

mental or generalized myoclonic movements of a repetitive and rhythmic nature.

The mechanisms underlying these forceful motor outbursts are little understood. Even anatomical sites of central nervous system damage which may be accompanied by this clinical symptom are far from clear. Myoclonus, for example, can be prominent during life, although careful necropsy reveals no unequivocal evidence of underlying lesions.⁹ On the other hand, certain encephalitides and progressive encephalopathies with striking myoclonic features may be associated with diffuse pathological changes throughout the entire central nervous system.¹⁹ In only a few specific situations is there good evidence that myoclonus results from structural damage to fairly well-defined regions,²⁰⁻²⁶ and these have ranged from cerebral cortex to spinal cord. On the whole, therefore, definitive study in human material of these myoclonic movements has of necessity been limited, and, by its very nature, lacking in precision.

Recently, encephalomyelitis has been produced in cats by infection with Newcastle disease virus.^{27,28} The incubation period and pattern of development vary somewhat with different routes of inoculation, and on clinical and anatomical grounds it is possible to delineate certain preferential pathways of viral spread. Predominant histological damage is found in certain nuclei at brain stem and spinal cord levels—cerebral cortex is uniformly spared. Forceful segmental and generalized repetitive myoclonus, strikingly similar to that encountered in human disease, is a prominent clinical feature of the illness. Certain definitive acute experiments have, therefore, been performed prior to and

Accepted for publication March 12, 1958.

Kenny Foundation Scholar (Dr. Luttrell).

This investigation was supported by research grant E-1230 from the National Institutes of Health, U. S. Public Health Service.

This paper was presented in part at the 82d Annual Meeting of the American Neurological Association in Atlantic City, June 18, 1957.

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during the period of active myoclonic activity initiated in cats by this viral infection. It is the purpose of this paper to describe the results of these studies and consider what light they may cast on mechanisms underlying these involuntary repetitive movements. Certain additional features have already been defined through intraventricular inoculation of virus and pharmacological agents.²⁹

Materials and Methods

Thirty-three previously healthy kittens or adult cats were used. All developed encephalomyelitis with rhythmic myoclonus after inoculation with Newcastle disease virus by various routes.²⁸ All were observed clinically and, in many instances, photographed cinematographically.

In eight cats, prior to inoculation, paired mid-frontal and posterior parietal silver disc electrodes were aseptically implanted, through burr holes, on the dura and fixed solidly in position with auto-polymerizing resin. Leads from these electrodes ran posteriorly to the nape of the neck. There they emerged through the skin and were attached to a leather collar. By this means standard electroencephalograms, without anesthesia, were made daily before and during the encephalomyelitis. Concomitant electromyographic discharges were recorded through paired insulated needle electrodes placed in appropriate skeletal muscles.

Before infection, laminectomy was performed under aseptic conditions in seven cats. In four of these, unilateral deafferentation of one hindlimb was achieved by intradural section of dorsal roots from L3 to S3, inclusive. In the other three animals, the spinal cord was hemisectioned at the T9 level. From two to three weeks postoperatively, all seven cats were inoculated with virus into thoracic spinal cord just above the site of previous operation.

During the stage of active rhythmic myoclonus, 25 of the 33 animals were anesthetized with ether. One or more complete acute transections of the neuraxis were then performed at various levels of spinal cord and upper brain stem. In one animal with chronic unilateral hindlimb deafferentation, the opposite leg was acutely deafferented, from L3 to S3, and the spinal cord then transected at the L3 level.

Results

A. Clinical Pattern of the Myoclonus.—Several clinical patterns of segmental or generalized rhythmic myoclonus differing largely in sequence of spread, and dependent

on route of inoculation, were described in a previous communication.²⁸ They may, therefore, be mentioned only briefly, and in a summary fashion. They fall into three main groups.

1. After intracerebral, intraocular, or intranasal inoculation, myoclonic movements first appeared in muscles of the head, neck, and forequarters. Only later in the progress of the illness did they spread to involve musculature of the trunk and hindlimbs.

2. When virus was injected into cervical spinal cord, the resultant myoclonus developed first in the forelimbs, before extending later to the hindquarters and medullary-innervated muscles. In most of these, rhythmic flexor spasms in fore- and hindlimbs were synchronous. In a few animals, however, flexor movements in the fore extremities were succeeded immediately by extensor thrust of the hindlimbs.

3. Lower thoracic cord inoculations led to primary myoclonic involvement of the hindlimbs. Only later did musculature of the forequarters share in these movements.

Myoclonus induced through infection by any of these routes was consistently reduced in rate and force by asphyxia. When tracheal obstruction was continued for several minutes, the movements ceased. With prompt restoration of pulmonary ventilation, the movements returned to their previous rate and vigor. Light ether anesthesia was without effect on the myoclonus. When deeper, the movements were abolished, only to return in full activity when anesthesia lightened.

B. Electroencephalography and Electromyography During the Myoclonus.—Active myoclonic movements were accompanied by serial outbursts of repetitive action potentials in the affected muscles (Fig. 1B). In contrast, electroencephalograms recorded during the stage of generalized rhythmic myoclonus differed in no way from those taken during previous normal periods (Fig. 1A, B). In two cats with terminal generalized convulsions there was diffuse convulsive electroencephalographic activity solely at that stage (Fig. 1C).

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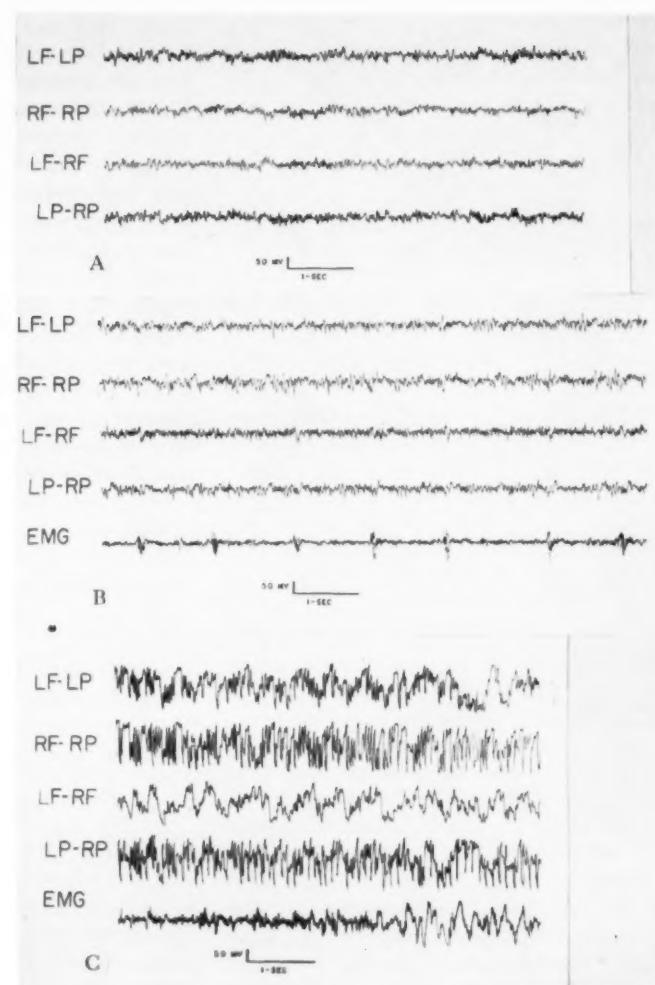


Fig. 1.—Electrode placements: *LF*, *RF*, left and right frontal; *LP*, *RP*, left and right parietal; *EMG*, electromyogram recorded from one forelimb.

A, control electroencephalogram before virus inoculation; *B*, electroencephalogram and electromyogram during stage of generalized rhythmic myoclonus; *C*, electroencephalogram and electromyogram in cat with terminal generalized convulsions.

C. Effects of Prior Deafferentation and Hemisection of Spinal Cord.—One leg in each of four cats was deafferented aseptically by section of the dorsal roots from L3 to S3, inclusive. Three weeks later, after virus inoculation into midthoracic spinal cord, myoclonus developed simultaneously in the two hindlimbs, and at the same rate. On the chronically deafferented side, however, hindlimb displacement with each myoclonic movement was considerably greater. Moreover, this difference in amplitude persisted after subsequent acute transection of the cervical or thoracic spinal cord. In one of

these animals additional acute intradural section, on the previously intact side, of all dorsal spinal roots from L3 to S3, followed by spinal cord transection at L3 level, failed to alter the character or rate of the myoclonus in either hindlimb.

In contrast were the findings in three animals inoculated intraspinally rostral to the site of prior lower thoracic hemisection of spinal cord. Myoclonus, when it emerged, began at the same time in the two legs but was considerably reduced in force and amplitude in the hindlimb ipsilateral to the hemisection.

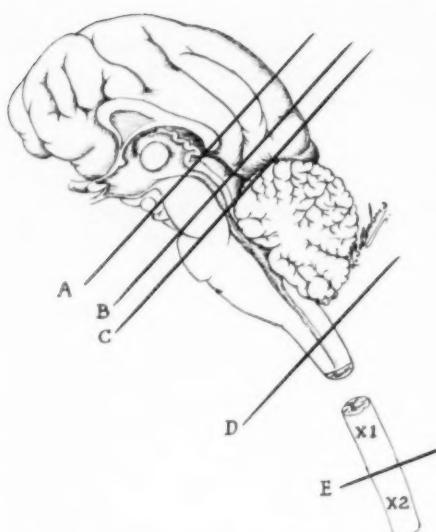


Fig. 2.—Illustration of brain and spinal cord, showing anatomical sites of acute transection of the neuraxis in cats with segmental or generalized myoclonus. The number of transections performed at each level was as follows: *A*, supracollicular, 4; *B*, midcollicular, 9; *C*, infracollicular, 4; *D*, cervical cord (Cl) level, 13; *Ex1*, midthoracic after virus inoculation into cervical cord, 6; *Ex2*, midthoracic after virus inoculation into low thoracic cord, 7.

D. Effects of Acute Transection of Brain Stem and Spinal Cord.—Brain stem and spinal cord were acutely transected at various levels during the active stage of generalized myoclonus. The sites and numbers of these operations are illustrated diagrammatically in Figure 2. The effects on myoclonus may be described briefly.

1. In 17 cats infected through cranial routes, acute severance at midbrain and upper pontine levels was, with one exception, without effect on rate, distribution, or character of the myoclonic movements. Indeed, in four animals the myoclonus was sufficiently intense to overcome strong extensor rigidity.

2. Thirteen similarly infected cats were made acutely spinal by high cervical transection at the level of the atlanto-occipital junction. In all but one, the character, distribution, and rate of the myoclonus in limbs and trunk were unaltered. Complex spinal reflexes were active. Recurrent spontaneous

scratch reflexes were observed. Crossed extensor reflexes were expressed through enhanced myoclonus in the extended limb. These spinal animals were able, without artificial respiration, to maintain adequate pulmonary ventilation for hours solely by myoclonic contractions.

3. Certain additional acute transections were performed in animals in which the myoclonus resulted from virus inoculation directly into spinal cord. In six cats infected in the cervical region, the myoclonic movements developed initially, as described above, in the forelimbs, with later involvement of the hindquarters. Midthoracic cord transection then abolished the myoclonus completely in the lower extremities but had no effect on muscular contractions in the forequarters.

Contrariwise, in seven cats with inoculation into midthoracic or lumbar spinal cord, myoclonus made its first appearance in the hindlegs, with only subsequent spread to forelimb musculature. In these animals, acute high thoracic transection abolished the movements in the forequarters, leaving those in the hindlimbs unchanged.

Comment

Previous studies^{27,29} have shown that Newcastle disease virus encephalomyelitis in cats is accompanied by segmental or generalized rhythmic myoclonus. On histological examination, cerebral cortex is essentially normal. In contrast, there is preferential damage to certain brain stem nuclei, as well as to middle and ventral zones of gray matter in the spinal cord. These findings suggest strongly that this form of myoclonus results from events occurring at brain stem or spinal level. The experiments described in the present communication were designed with a double purpose, namely, to examine functionally the relevance of this histological localization, and to seek information on the nature of the mechanisms underlying the myoclonic movements.

Correlation of general functional localization with that indicated by histological means

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has been unequivocal. During active generalized myoclonus, electroencephalograms were similar to those obtained before infection. Moreover, acute decerebration did not alter the character or pattern of the myoclonus. It seems evident, therefore, that the "pathophysiological" changes responsible for these myoclonic discharges originate either at brain stem or spinal cord level, or at both.

The present study shows clearly that all the necessary integrants for development of myoclonus exist at the spinal level, since coordinated myoclonic contractions of forequarters, trunk, and hindquarters were unchanged by high spinal cord transection. Using a similar approach, Feldberg and Luttrell²⁹ have shown that with combined midbrain and high cervical transection, tongue myoclonus persists from discharges originating in isolated brain stem. Apparently, then, similar patterns of myoclonus, differing only in distribution, can result from effects of virus at either of these levels of the central nervous system.

The present experiments also serve to resolve discrepancies encountered in correlating the clinical aspects of encephalomyelitis resulting from intraspinal infection and the lesions found histologically in these animals during the early stages of the illness. After inoculation of virus into lumbar or lower thoracic cord, myoclonus first develops in the hindquarters, but soon thereafter the forelimbs become involved as well. Contrariwise, cervical spinal cord inoculations are followed by myoclonic movements which appear initially in the forelimbs, followed soon by spread to the hindquarters. After lumbar or thoracic infections, however, pathological lesions are not found in cervical spinal cord during early stages of myoclonus. Likewise, with cervical inoculations no histological abnormalities are detectable in the lumbar region of the spinal cord at similar times. It was not surprising, therefore, to find that the myoclonic movements in those limbs remote from the site of inoculation were abolished by acute midthoracic spinal cord transection, although myoclonus in the adjacent limbs remained unchanged. Clearly,

these observations indicate strongly that the spread of myoclonic involvement under these circumstances is due not to extensive viral dissemination within the spinal cord but, rather, to the participation of complex propriospinal neural mechanisms. The careful studies of Lloyd and McIntyre³⁰ provide evidence for the existence of such possible integrating mechanisms in spinal cats between cervical and lumbar parts of the spinal cord. They do not, however, provide much information on the characteristics of these integrating systems. In the present studies, prior hemisection of the spinal cord reduced the amplitude of myoclonic movements on the same side, but did not abolish them. The inference is strong, therefore, either that the coordinating mechanisms in the spinal cord involve pathways with bilateral connections or that crossed effects occur at segmental levels.

Hitherto, precise functional analysis of the effects of virus on excitable tissue has been confined to those of pseudorabies on sympathetic ganglia^{31,32} and of poliomyelitis virus on motoneurons.³³ The nature of the present experiments was not such as would allow objective demonstration of excitatory action of Newcastle disease virus on cells within the central nervous system. It is at least reasonable, however, to assume that such occurs, and that the direct irritant effect of the virus on interconnected pools of motoneurons or interneurons leads to the repetitive discharges of myoclonus. The resultant patterns of integrated muscular contractions would then be governed only by the anatomical arrangements and degree of organization present at different levels of the neuraxis.

Less clear, however, are mechanisms responsible for the periodicity of this myoclonus. It might be thought that the inherent rhythmicity is regulated in some manner by segmental excitatory or inhibitory influences from the periphery. Indeed, Gray and Lissmann³⁴ and Lissmann³⁵ have presented some evidence to suggest that a persistent locomotory rhythm in the toad and in spinal dogfish depends on some degree of integrity

of afferent inflow. Such regulation from the periphery does not, however, appear to be operative in the type of rhythmic discharge under study here. Certainly, the myoclonic movements in chronically deafferented limbs differed from those on the opposite side only in that their amplitude, unlimited by myotatic inhibitory influences, was greater. There is, moreover, even more convincing evidence for independence of the rhythmicity of the myoclonus from afferent inflow. After total intradural deafferentation of both hindlimbs, and surgical separation from higher regions of the neuraxis, the myoclonic movements in the hindquarters persisted unchanged. It seems evident, therefore, that an inherent intraspinal process governing rhythmic activity is operative here. Others, using different forms of coordinated motor discharge, have come to similar conclusions.³⁶⁻⁴⁰ Indeed, it seems here that we have yet another instance where repetitive discharge from individual cells in an isolated segment of central nervous system is, in some obscure manner, integrated to create a coordinated motor discharge of a rhythmic nature.

Summary

Segmental or generalized rhythmic myoclonus regularly developed in cats after inoculation of central nervous system with Newcastle disease virus. Its pattern varied with the anatomical site of inoculation.

Electroencephalograms showed no evidence of cerebral dysrhythmia coexistent with the clinical myoclonus.

Light ether anesthesia had no effect on the myoclonus. Asphyxia, however, consistently reduced its rate and force.

Acute brain stem transections were without effect on the myoclonus. Chronic hemisection of thoracic cord and acute high cervical transection did not change the character or rate of the repetitive muscular contractions. In these spinal animals, myoclonic movements were adequate to maintain pulmonary ventilation for many hours.

Chronic unilateral or bilateral intradural deafferentation from L3 to S3 and subsequent isolation of lumbosacral cord did not alter the hindlimb myoclonus.

These experiments indicate strongly that the myoclonic movements were caused by some "pathophysiological" change occurring at the organization level of either brain stem or spinal cord or both.

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Study of Excretion of 5-Hydroxyindoleacetic Acid in Mental Patients

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Introduction

5-Hydroxyindoleacetic acid (5-HIAA) has recently been shown to be a major end-product of 5-hydroxytryptamine (serotonin, enteramine) metabolism.^{1,2} Thus, excretion of this substance is an adequate indicator of serotonin metabolism under some conditions. Many studies have already been made with serotonin, and several reviews discuss such work.^{3,4} Even a superficial consideration of all aspects of serotonin is not possible here, and only a brief summary of work relating serotonin to brain function will be presented. The concept that serotonin is involved in brain function is strongly supported by Woolley and Shaw,^{5,6,7} who used structural analogs of serotonin, and by Gaddum and co-workers,^{8,9} who employed antagonists of that neurohormone. This concept is also held by Brodie and his group,¹⁰⁻¹² who studied the effect of the Rauwolfia alkaloids and other compounds on the release of serotonin from various body sites in animals.

This laboratory was especially interested in the observations of the Brodie group, who found that the release of serotonin was limited to Rauwolfia drugs with tranquilizing action.^{11,13} The release of serotonin from body sites by reserpine has been evidenced by a drop in serotonin content in the brain, blood, and intestine of animals,^{10,14,15} and in the blood of man.¹⁴⁻¹⁶ It has also been demonstrated by an increase in the urinary excretion of 5-HIAA in animals.^{17,18} However, massive doses of reserpine were used

in the experiments in which the urinary excretion of 5-HIAA was studied.

Up to the time our study was initiated, no experiments with humans had been reported dealing with the effect of reserpine on the urinary excretion of 5-HIAA. However, papers describing such studies have recently appeared in the literature. Haverback et al.¹⁹ did not observe any effect of reserpine administration on the urinary excretion of 5-HIAA, while Fraser and co-workers²⁰ found a definite increase in the excretion of 5-HIAA in the humans they studied.

Our laboratory is fortunate in having at its disposal two metabolic wards of 12 or 13 mental patients each. The patients have been carefully selected for long-term studies on aging and mental disease and are available for short-term experiments. Such an arrangement made possible the collection of 24-hour urine specimens and the quantitative study of the effect of reserpine upon the urinary excretion of 5-HIAA in these patients.

Experimental Procedure

The subjects used in this study are male patients from our two metabolic wards. One ward is made up of schizophrenics and the other of mental defectives. Each experiment was conducted on a group of four to six patients in order to ensure maximum supervision in the matter of urine collections.

The urine samples were collected in bottles containing toluene to minimize exposure of the urine to air. When collection was complete, the urine volume was determined and an aliquot placed in the refrigerator for subsequent assay. The creatinine content of the urine samples was measured by the Folin modification²¹ of the Jaffe procedure. The values thus obtained served as a check of the completeness of the 24-hour collection and were

Received for publication Jan. 6, 1958.

Present Address: Memorial Hospital, Springfield, Ill.

A preliminary report of this work was presented at the 41st Annual Meeting of the American Physiological Society, Chicago, April 15-19, 1957.

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essentially unchanged whether or not reserpine was being administered.

5-HIAA was extracted and assayed by a modification of Udenfriend's procedure.²⁰ We found it advisable to run internal standards with each sample assayed, since the recovery of 5-HIAA added to urine was incomplete. In addition, the recovery varied from sample to sample, and especially from patient to patient. The recovery usually ranged from 55% to 75%. Therefore, all values for 5-HIAA were calculated so as to compensate for the varied recoveries obtained. All data are expressed in milligrams of 5-HIAA per 24 hours and milligrams of 5-HIAA per gram of creatinine.

The placebo control values were determined before reserpine medication, except for one group of patients, in which these values were measured 10 weeks after cessation of the first course of reserpine. Practically all values were obtained from samples collected on successive days.

The patients were placed on a course of reserpine for at least one week; then the medication was discontinued. Five to nine weeks after cessation of medication, the patients received another course of reserpine. In all cases 2 mg. of reserpine was administered twice daily to each patient. When not on medication, the patients were always kept on placebo. Both reserpine and placebo were given by mouth.

Results

Experiment 1.—One group of experimental subjects consisted of six schizophrenic patients (one simple, one hebephrenic, one catatonic, three paranoid). This group was placed on three courses of reserpine, and data were obtained during the first and third courses. In the first course the excretion of 5-HIAA was determined only during reserpine medication. In the third course the excretion of 5-HIAA was measured not only during reserpine administration but also immediately after its cessation. Table 1 presents the results of this experiment. An increase of 5-HIAA excretion of almost 25% over placebo control levels was noted on the first day of medication during the first experimental treatment with reserpine. The excretion of 5-HIAA after the first day showed no significant change from the control values. There was again a marked rise on the first day of medication during the third course of treatment. This rise amounted to more than 30%. After the first day the excretion of 5-HIAA

TABLE I.—Urinary Excretion of 5-Hydroxyindoleacetic Acid: Experiment 1

Subject *	Placebo Control	First Course			Third Course					
		Reserpine 2 Mg. b. i. d.			Reserpine 2 Mg. b. i. d.			After Cessation of Reserpine		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 8
Milligrams 5-HIAA per 24 Hours										
1	4.70	5.84	6.20	4.60	5.68	8.62	6.33	4.99	4.77	8.55
2	5.50	6.47	6.29	6.05	6.95	9.80	6.19	6.88	8.50	5.65
3	5.45	6.14	9.43	5.55	5.88	8.81	8.05	7.95	4.01	5.57
4	6.37	7.17	9.50	6.46	7.57	7.17	7.49	6.52	6.30	7.63
5	5.90	5.59	7.74	7.28	6.28	7.69	8.19	5.94	5.48	6.21
6	11.8	10.6	11.1	9.02	9.41	11.8	9.00	8.60	11.2	11.4
Ave.	6.62	6.97	8.38	6.49	6.96	8.98	7.54	7.18	6.75	8.87
Milligrams 5-HIAA per Gram Creatinine										
1	4.05	3.62	5.80	4.07	4.65	5.64	5.40	3.67	2.93	5.39
2	3.04	3.54	5.76	4.26	4.55	5.66	3.73	3.76	4.55	3.54
3	4.78	4.29	5.65	4.55	4.74	7.73	6.55	6.21	4.61	4.89
4	5.26	4.66	4.90	4.90	5.65	4.69	5.00	3.90	4.07	5.23
5	3.60	3.04	4.94	4.25	4.07	4.77	4.52	2.98	3.26	3.82
6	9.36	6.13	7.45	6.68	7.35	8.32	7.44	6.59	8.06	8.94
Ave.	5.02	4.22	5.75	4.77	5.17	6.14	5.44	4.69	4.70	5.90

* Patient 1 was diagnosed as simple schizophrenic; Patient 2 as catatonic; Patient 3, 4, and 5, as paranoid, and Patient 6, as hebephrenic.

TABLE 2.—Urinary Excretion of 5-Hydroxyindoleacetic Acid: Experiment 2

Subject *	Placebo Control	First Course					Second Course				
		Reserpine 2 Mg. b. i. d.			After Cessation of Reserpine		Reserpine 2 Mg. b. i. d.			After Cessation of Reserpine	
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 7	Day 1	Day 2	Day 3	Day 8
Milligrams 5-HIAA per 24 Hours											
7	12.9	12.6	18.3	9.72	10.0	9.25	10.9	11.9	13.3	10.4	12.5
8	10.6	9.94	12.1	9.05	8.19	9.93	8.88	7.44			
9	7.90	7.93	10.9	9.35	6.80	5.09	7.05	7.19	12.1	8.75	8.05
10	6.20	6.49	5.63	6.30	5.08	6.02	4.35	3.88	12.7	7.37	6.04
11	7.40	6.52	9.98	7.10	7.07	5.70	5.16	5.78	11.2	6.29	5.44
Ave.	9.00	8.70	11.4	8.30	7.43	7.20	7.27	7.24	12.3	8.20	8.01
										7.71	8.66
											8.50
Milligrams 5-HIAA per Gram Creatinine											
7	8.90	8.40	12.4	7.30	8.00	5.04	5.50	7.54	14.4	8.14	8.87
8	8.23	6.41	7.61	5.88	5.97	6.85	6.08	6.57			
9	6.42	6.71	9.40	6.69	6.48	4.10	4.27	5.84	9.39	7.75	6.44
10	3.56	3.60	5.36	3.96	3.48	3.94	3.13	3.60	7.94	3.92	3.97
11	4.77	3.22	5.25	3.95	4.48	3.58	2.90	3.50	6.87	3.36	3.38
Ave.	6.38	5.67	8.00	5.55	5.68	4.70	4.38	5.41	9.65	5.79	5.67
										5.01	5.79
											5.88

* Patient 7 was diagnosed as hebephrenic-paranoid; Patient 8, as hebephrenic, and Patient 9, 10, and 11, as simple schizophrenic.

diminished, but still remained slightly above the placebo level. Following cessation of reserpine medication the excretion of 5-HIAA remained at the control level. However, on the eighth day a large increase occurred. As will be observed from later experiments, this was the only instance of such a rise other than on the first day of reserpine, and we have no explanation for this result.

Experiment 2.—In this experiment a different group of five, schizophrenic patients was used (three simple, 1 hebephrenic, 1 hebephrenic-paranoid). This group was placed on two courses of reserpine, and data were obtained during and after cessation of medication in both courses. Table 2 lists the results of this experiment. During the first course we noted a rise of approximately 30% in the excretion of 5-HIAA on the first day of medication. After cessation of medication, the excretion of 5-HIAA fell below the placebo control level. The greatest reduction amounted to 18% calculated on the basis of 24-hour excretion, and 27% calculated on the basis of creatinine excretion. During the second course of reserpine, there was an even larger increase in the excretion of 5-HIAA on the first day of medication.

This rise amounted to 45% calculated on the basis of 24-hour excretion, and to 70% calculated on the basis of creatinine excretion. 5-HIAA excretion again fell to placebo control levels or less after the first day of medication and after cessation of medication.

Experiment 3.—Six mentally defective patients were used for this experiment, which was conducted in the same manner as Experiment 2. Table 3 lists the results obtained in this experiment. In this group excretion of 5-HIAA on the first day of initial reserpine administration rose 52% calculated on the basis of 24-hour excretion, and 37% calculated on the basis of creatinine excretion. A fall in 5-HIAA excretion was again noted after cessation of medication, the greatest fall amounting to 25% calculated either way. During the second course of reserpine the percentage rise in the excretion of 5-HIAA on the first day of medication was practically the same as during the first course. After the first day, and after cessation of reserpine administration, the excretion of the serotonin metabolite again reached placebo levels or less.

The Figure summarizes the results of these three experiments. It can be seen that the most pronounced effect of reserpine on

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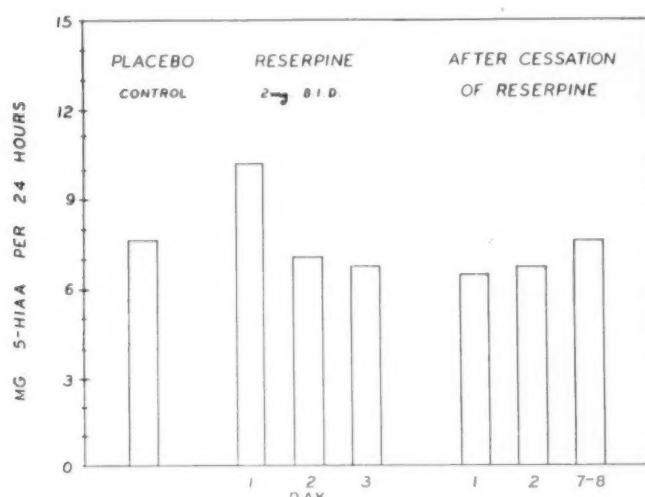
TABLE 3.—Urinary Excretion of 5-Hydroxyindoleacetic Acid: Experiment 3

Subject *	Placebo Control	First Course						Second Course					
		Reserpine 2 Mg. b. i. d.			After Cessation of Reserpine			Reserpine 2 Mg. b. i. d.			After Cessation of Reserpine		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 7	Day 1	Day 2	Day 3	Day 1	Day 2	Day 8
Milligrams 5-HIAA per 24 Hours													
12	5.35	6.22	8.35	6.95	8.16	5.57	5.07	6.92	12.3	6.02	5.50		6.85
13	9.53	8.35	14.1	6.10	3.97	6.38	6.12	6.58	13.5	5.80	6.07	5.19	6.57 6.84
14	8.61	8.42	12.5	9.84	9.30	7.23	6.49	6.78	11.1	7.92	6.70	7.32	12.3 7.45
15	5.71	4.21	9.30	6.69	5.74	4.91	4.40	4.45	6.76	6.29	5.15	5.35	2.32 6.62
16	6.17	5.35	7.06	6.12	5.45	5.14	4.87	6.30	8.97	5.90	5.50	5.70	7.55 6.32
17	10.7	9.16	15.5	3.50	7.68	6.29	5.98	5.99					
Ave.	7.68	6.95	11.1	6.53	6.72	5.92	5.49	6.17	10.5	6.39	5.78	5.89	7.18 6.82
Milligrams 5-HIAA per Gram Creatinine													
12	4.74	5.87	6.52	6.04	7.30	4.57	4.23	5.97	9.54	4.63	4.58		6.52
13	6.07	5.75	6.62	4.07	4.41	4.34	3.88	4.57	8.84	4.50	3.16	3.73	4.30 5.25
14	5.78	7.08	9.40	6.27	7.10	5.06	4.70	5.10	6.54	4.43	4.30	4.75	7.64 5.69
15	3.76	2.94	5.96	4.18	3.98	3.32	3.14	3.18	3.06	3.86	3.16	4.18	1.39 5.26
16	3.81	3.99	4.59	4.25	4.40	3.57	3.46	4.12	5.90	3.28	3.84	3.85	4.46 4.39
Ave.	5.07	5.23	7.07	4.46	5.33	4.16	3.88	4.45	6.96	4.14	3.81	4.13	4.45 5.42

* Subjects diagnosed as high-grade mental defectives.

the urinary excretion of 5-HIAA in these patients is the marked rise on the very first day of medication. This increase averaged 36% and occurred in almost all patients. Although this first-day response to reserpine varied over a relatively wide range, the increase was 30%-70% in nearly two-thirds of the urine samples.

Other Experiments.—An attempt was made to pinpoint the increase in the excretion of 5-HIAA by collecting the 24-hour urine in several fractions. However, the results obtained in a pilot experiment were inconclusive because of the much greater variation in the daily excretion of 5-HIAA occurring within the shorter collection



Average daily urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) in schizophrenic and mentally defective patients on reserpine, 2 mg. orally b. i. d., and on placebo before and after administration of reserpine. Summary of data from all experiments. Note increase in excretion of 5-HIAA on first day of reserpine medication.

periods. This was probably due in part to a greater difficulty in obtaining identical urine samples from day to day.

We were also interested in studying the effect of other tranquilizers, especially the phenothiazine derivatives, on the excretion of 5-HIAA in these patients. The first such drug we intended to use was chlorpromazine. However, some preliminary uses of this drug brought out an unforeseen difficulty. We found that when the urine of one patient placed on chlorpromazine was extracted and assayed for 5-HIAA, the recovery of authentic 5-HIAA added to the urine was lowered markedly. This was confirmed by placing four additional patients on chlorpromazine. The recovery of added 5-HIAA ranged from 6% to 35% and averaged 17%. This is quite low when compared with the usual recovery of 55% to 75%. Thus, low values for urinary 5-HIAA of chlorpromazine-treated subjects will be noted when using Udenfriend's procedure. These low values are probably due to a quenching of the color,²³ as occurred when the urine of a patient with malignant carcinoid on chlorpromazine was assayed directly.²⁴ In its present form this procedure cannot be used to determine whether or not chlorpromazine has any effect on the urinary excretion of 5-HIAA.

Comment

From the data presented it is evident that the most consistent effect of reserpine administration on the urinary excretion of the serotonin metabolite in our patients was a large rise on the first day of medication. This reflects an effect of reserpine on serotonin itself. From the work of Brodie et al.²⁵ it is logical to conclude that this effect consists in the displacement of serotonin from its binding sites by reserpine and an impairment of the binding sites, resulting in a greatly diminished capacity to bind serotonin. This excess-free serotonin then is susceptible to rapid conversion to 5-HIAA by amine oxidase. After this initial effect, the synthesis and breakdown of

serotonin in the body apparently reach equilibrium. After medication is stopped, serotonin is taken up again by its binding sites. However, this retention is too slow to be detected by measuring the urinary excretion of 5-HIAA.

We are unable to estimate by our experimental procedures how much, if any, of the excess urinary 5-HIAA reflects brain serotonin. Larger amounts of serotonin are present in the intestine and the blood, and these sites are known to be reduced in serotonin content in animals when sufficient reserpine^{10,14} is administered. However, since serotonin from the brain of animals can also be displaced,^{11,14,15} perhaps some of the excess urinary 5-HIAA does reflect brain serotonin. This seems especially likely since, in animals, brain serotonin is more sensitive to reserpine than the serotonin present in the largest depot, the intestine.^{11,14,15}

The rise in the excretion of 5-HIAA on the first day of reserpine medication was greater in the mentally defective patients than in the schizophrenic patients. However, sufficient data are not available to determine whether this interesting observation is significant.

It is tempting to relate these results to the clinical effect of reserpine. Brodie^{10,26} believes that the tranquilizing effect of reserpine is mediated through serotonin. However, reserpine must not exert its behavioral effect through the initial release of serotonin, since this effect of the drug in humans usually does not appear until several days after oral medication is initiated.²⁷ The question of how serotonin fits into the function of the nervous system is under intensive study in several laboratories. From our work we can only say that the change observed in the excretion of 5-HIAA reflects an effect of reserpine on the metabolism of serotonin in man.

Summary

Reserpine, 2 mg. twice daily, was administered to 11 schizophrenic patients and

EXCRETION OF 5-HIAA IN MENTAL PATIENTS

to 6 high-grade mentally defective patients. The excretion of 5-HIAA was increased on the first day of medication in both groups of patients.

The excretion of the serotonin metabolite after the first day of medication and after its cessation was reduced to premedication levels or less.

When these patients were given a second or third course of reserpine at a later date, the excretory pattern of 5-HIAA was essentially the same as during the first course.

The most consistent feature of the experiments was the marked rise in the excretion of the serotonin metabolite on the first day of reserpine medication.

Mrs. Joyce Appleby and Mrs. Carol Stewart gave technical assistance in the laboratory.

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Cognitive Changes Following Temporal Lobectomy for Relief of Temporal Lobe Epilepsy

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Problem

In a preliminary study by Meyer and Yates,¹ it was reported that after temporal lobectomy some intellectual changes take place and that evaluation of the effects of the operation requires a breakdown into dominant and nondominant groups. The present investigation is an attempt to confirm the tentative findings of the preliminary study on larger samples of dominant and nondominant patients, to define more closely the nature of deficits, and to assess long-term effects.

Tests and Testing Procedures

The three intelligence tests described in the preliminary study, i. e., the Wechsler-Bellevue Intelligence Scale, the Mill Hill Vocabulary Test, and Raven's Progressive Matrices, have been retained. Six new learning tests were designed in order to answer the problems concerning learning ability. The New Word Learning and Retention Test (NWLT) has also been retained, as it is the original test on which the deficit was detected. This test involves learning of definitions of unfamiliar words.

Each new test takes the form of a pair of associates, and the subjects are required to learn them to a criterion of three successful consecutive responses for each pair.

1. Auditory-Verbal-Recall (AVR) involves learning using the auditory modality, verbal material, and the recall mode of reproduction.

Accepted for publication April 15, 1958.

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This paper represents a summary of part of a thesis submitted to the University of London in part fulfillment of the requirements for the degree of Doctor of Philosophy. The reader interested in details of the present study may be referred to this thesis.²

2. Auditory-Verbal-Recognition (AVR_R) resembles AVR in every respect except that the recognition mode of reproduction is employed.

3. Visual-Verbal-Recognition (VVR_R) involves learning of pairs of words presented visually. The recognition method is used.

4. Visual-Design-Recognition (VDR_R) requires learning of pairs of designs presented visually and using the recognition method.

5. Visual-Design-Recall (VDR) involves learning of designs which are paired with pictures of common objects. On presentation of a picture of any object, the subject is required to reproduce the correct design by drawing from recall.

6. Tactile-Design-Recognition (TDR_R) consists of learning pairs of wire patterns by means of the recognition. The subject is blindfolded, and patterns are placed in his palms.

The total score on each test includes presentation of the list, presentations following wrong responses, and failures to respond within prescribed time limits. Each test has two equivalent forms, A and B.

The preoperative testing took place about 1 to 28 days before the operation (mean=4.84; S. D.=6.07). The first postoperative assessment was carried out about 20 to 35 days after the operation (mean=27.84; S. D.=3.01). The second postoperative testing took place 11 to 15 months following the operation (mean=12.35; S. D.=1.11). Form I of the Wechsler and Mill Hill tests was used preoperatively and one year postoperatively. Form II of these tests was given one month after the operation. The two forms of the learning tests were used interchangeably among the three assessments, as were the intelligence tests. The same forms, however, were not always given first. Thus, equal numbers of patients had these tests in the orders ABA and BAB. This procedure was adopted because the equivalence of the forms was unknown.

Subjects

Results on a total of 25 patients are reported in this study. Table 1 describes the patients with respect to various relevant factors. A more detailed description of these patients has been given elsewhere.²

TABLE I.—Description of Patients*

No.	Sex	Age	Age At Onset of Fits, Yr.	Duration of Fits, Yr.	Handedness	EEG Evidence	Side of Operation and Dominance	Extent of Operation, Cm.	Dysphasic Disturbances (Nominal)	Visual Field Defects (Partial Homonymous Hemianopsia)	Other Defects (Transient)
Dominant Cases											
1	M	27	13	14	R	L. temporal	L	7.0	Moderate	Right upper quadrantic	Nil
2	F	38	8	30	R	L. temporal+ (R. temporal)	D-H	7.0	Marked	Severe right	Partial left ptosis+diplopia
3	M	12	3	9	R	L. temporal+ (R. temporal)	D-H	5.0	Nil	Minimal right lower quadrant	Nil
4	F	17	8	9	R	L. temporal+ (R. temporal)	D-H	7.0	Mild	Right upper quadrantic	Nil
5	F	18	4	14	R	L. temporal	D-H	5.5	Moderate	Severe right	Partial left ptosis+diplopia
6	F	20	13	7	R	L. temporal	D-H	6.5	Mild	Right upper quadrantic	Diplopia
7	F	34	16	18	R	L. temporal	D-H	7.0	Mild	Severe right	Complete left ptosis
8	M	35	22	13	R	L. temporal	D-H	6.5	Marked	Right upper quadrantic	Nil
9	M	46	31	15	R	L. temporal	D-H	6.0	Moderate	Right upper quadrantic	Mild right hemiparesis
10	M	17	2	15	R	L. temporal	D-H	6.5	Mild	Right upper quadrantic	Diplopia
11	M	23	11	12	R	L. temporal+ (R. temporal)	D-H	5.5	Mild	Right upper quadrantic	Mild right hemiparesis
12	M	13	11	2	R	L. temporal+ (R. temporal)	D-H	6.0	Moderate	Minimal right upper quadrantic	Nil
13	M	27	3	24	R	L. temporal	D-H	4.5	Nil	Minimal right upper quadrantic	Nil
14	M	41	11	30	R	L. temporal	D-H	6.0	Mild	Right upper quadrantic	Nil
Nondominant Cases											
15	F	28	22	6	R	R. temporal+ (R. hemisphere)	R	7.0	Nil	Minimal left upper quadrantic	Nil
16	F	21	2	19	R	R. temporal	R	6.5	Nil	Minimal left upper quadrantic	Nil

17	F	17	7	10	R	R. temporal	R N-DH	6.5	Minimal left upper quadrant
18	M	29	15	14	R	R. temporal+ (R. frontal)	R N-DH	8.0	Nil
									Complete right paresis
Dominant Cases									
19	M	19	6	13	R	R. temporal+ (L. temporal)	R N-DH	7.0	Nil
20	F	19	12	7	R	R. temporal+ (L. temporal)	R N-DH	6.0	Nil
21	M	51	5	46	R	R. temporal	R N-DH	8.0	Severe left
22	F	35	34	1	R	R. temporal	R	7.0	Severe left
Doubtful Cases									
23	F	14	3	11	Ambidex- trous	L. temporal	L D-D	4.5	Minimal right upper quadrant
24	M	35	23	12	L	R. temporal+ (L. temporal)	R D-D	7.0	Nil
25	M	17	4	13	L	L. temporal+ (R. temporal)	L D-D	5.0	Minimal right upper quadrant
									Left hemiplegia
									Diplopia

* R. temporal=right temporal focus; L. temporal, left temporal focus; L. temporal+(R. temporal)=bilateral foci with left focus predominant; D-H = dominant hemisphere; N-DH = nondominant hemisphere. D-D = doubtful dominance.

Visual field defects were assessed on the perimeter Bjerrum screen and dysphasic disturbances on the common-object-naming test. The patients were divided into "dominant" and "nondominant" groups according to recent findings.^{3,4} All unequivocally right-handed subjects who were operated upon on the left side were classified as dominant, while right-handed subjects with right-sided operations were described as nondominant. All the left-handed and ambidextrous patients were called doubtful with regard to dominance, and they were included in the nondominant group for statistical analysis of the result.

The preponderance of left-sided abnormalities is in agreement with previous findings.^{4,5} The entire battery of tests was given to all subjects before and one month after the operation, except for VDR, and 10 dominant and 7 nondominant subjects (5 nondominant and 2 of doubtful dominance) were retested a year after the operation. The two groups did not differ significantly in respect to such variables as age, age of onset, and duration of seizures, extent of operation, and testing times.

Predictions and Expectations as to Possible Test Results

I have shown⁶ that the literature on brain damage does not permit a clear orientation in this field. Despite a vast amount of psychological studies of neurological patients, no acceptable theory of brain functioning and organization has emerged. Up to the present time the findings on localization of functions are in general inconsistent and very often contradictory. The same applies to the findings on the temporal lobe.

The most consistent finding is that temporal lobe subjects manifest, as a group, impairment on verbal tasks as compared with nonverbal tasks.^{1,5,7}

Several studies reported deficits on memory processes, particularly those requiring acquisition of verbal material using the auditory modality.⁷⁻¹⁰ Some evidence indicated that bilateral medial temporal resection results in a persistent and generalized impairment of ability to record current experience.¹¹

A number of findings demonstrated an impairment on various tasks involving the auditory modality, i. e., auditory pattern association¹²; timing test, flutter fusion, and pattern discrimination,¹³ and condition-

ing of alpha activity to a sound stimulus.¹⁴ However, not all auditory functions appear to be impaired after temporal lobe injury.^{14,15}

The above studies did not attempt to evaluate results in terms of the laterality of abnormalities, and some evidence indicates that a breakdown into left- and right-sided-lesion groups would have produced somewhat different results. In the temporal lobe aphasia the receptive components of speech are impaired, with difficulty in understanding and in retention of spoken language. Consistent with this, a number of findings, summarized elsewhere,¹⁶ demonstrated that patients with the dominant-hemisphere lesions are relatively poor at verbal tasks; those with the nondominant-hemisphere lesions, on the other hand, do worse at manipulation of spatial or spatio-temporal relationship. Heilbrun¹⁷ confirmed the verbal deficit in right-sided-lesion cases. In contrast to the latter finding, several reports¹⁸ demonstrated that right temporal lesions result in deficits on tests of space patterning.

In view of the above, the dominant-temporal-lobe cases would be expected to show deficits on verbal tests and tests requiring the use of the auditory modality; the nondominant-temporal-lobe cases would be expected to manifest impairment on non-verbal tests, particularly those involving organization of spatial relationship. A possible explanation of the discrepancy between the findings in temporal lobe cases and those in left- and right-sided-lesion cases with regard to verbal-performance pattern is that epileptic EEG abnormalities tend to occur more frequently in the left than in the right temporal lobe.^{4,5,13} Thus, the verbal-performance-score pattern in groups of temporal lobe involvement may largely depend on the composition of the groups with regard to laterality of involvement. This hypothesis has been supported.¹⁶

Apart from the above studies, various findings related to the temporal lobes have been reported, but these are inconsistent.

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Milner¹⁸ showed her temporal lobe cases, as a group, to be inferior to her controls, both before and after temporal lobectomy, on visual tasks involving complex pictorial material. She attributed visual integrative functions exclusively to the temporal lobes. However, this view has not been supported.²⁰ Impairment on complex tactal tasks has been reported,²¹ but other investigators did not confirm it.^{20,21,23}

Most of the above studies are subject to the usual criticism,⁶ and the research so far available has not conclusively established the dependence of any cognitive function on the temporal lobes. On the basis of the above discussion, only tentative expectations were formulated as regards changes following the operation.

An examination of relevant literature indicates that the I. Q. tests used in the present study reach an acceptable level of reliability and validity, and alternative forms are more or less equivalent. Practice effects were taken into consideration.

Results

Preoperative Results.—Except for the Mill Hill and AVR_g tests, the dominant and nondominant groups may be considered equivalent with regard to intelligence level and learning ability. However, the dominant group tended to produce apparently lower scores on all measures.

One-Month Postoperative Results.—Intelligence Level: The nondominant group produced no significant changes on any measures, and, in fact, increased their scores on the Wechsler Verbal Scale and Full-Scale I. Q. and the Progressive Matrices. These increases may be due to practice effects. As regards the Performance Scale, there was a slight, though insignificant, decline.

The dominant group declined significantly on the verbal tests and on the Wechsler Performance Scale. The Matrices test, however, showed insignificant gain, which, again, may be due to practice effect.

The dominant group declined somewhat in all subtests of the Wechsler Scale, itself

an indication of a significant trend. The nondominant group produced no constant pattern of change; the two subtests most closely related to visuospatial ability both showed an apparent increase in mean scores.

The highly significant decline of the dominant group on verbal tasks appeared to be due mainly to inferior responses; i. e., they were marked by circumlocution and description. Finally, both groups showed a slight, but insignificant, trend toward an increase in the time required to complete the Matrices.

Learning Ability: The dominant group manifested a striking deficit on the three auditory verbal learning tests. The remaining tests showed no significant or consistent changes.

The nondominant group, on the other hand, produced no significant changes on any of the tests, except on AVR_g, where a significant gain was present. On the remaining tests, slight gains were in evidence.

One-Year Postoperative Results.—Table 2 presents mean changes on all measures between the second and the third assessment. Table 3 compares the scores of the first and third assessments.

Intelligence Level: The nondominant group showed gains on all tests in the third as compared with the second assessment. These attained significance on all scales of the Wechsler test and may well be due to practice effects. The dominant group demonstrated apparent improvements on all tests, however, except for the Mill Hill; these failed to reach significance. As compared with the preoperative scores, this group still showed impairment on most measures.

Learning Ability: The nondominant group produced no significant changes on any of the learning tests and, in fact, progressively increased its scores on most tests. The dominant group showed insignificant gains on the auditory learning tests; however, the level of performance was still significantly below the preoperative one. The remaining tests showed no significant or consistent changes.

TABLE 2.—Statistical Analysis of Results: Significance of Mean Differences Between One-Month and One-Year Postoperative Test Scores

	Dominant Group (N=10)						Nondominant Group (N=7)					
	1 Mo.		1 Yr.		Postoperative		1 Mo.		1 Yr.		Postoperative	
	Mean	S. D.	Mean	S. D.	A *	Probability	Mean	S. D.	Mean	S. D.	A	Probability
Wechsler Verbal Scale I. Q.	64.40	16.32	80.20	16.03	0.456	$P > 0.10$	108.43	25.92	112.86	24.82	0.257	$0.05 > P > 0.02$
Wechsler Performance Scale I. Q.	94.40	13.25	102.00	13.15	0.306	$0.10 > P > 0.05$	103.14	25.52	111.43	21.89	0.289	$0.05 > P > 0.02$
Wechsler Full-Scale I. Q.	86.60	15.05	95.20	14.87	0.349	$0.10 > P > 0.05$	106.05	106.57	27.23	113.14	24.07	$0.05 > P > 0.02$
Mill Hill raw scores	33.90	10.30	37.60	10.51	0.125	$P > 0.05$	50.71	24.49	52.00	23.14	0.531	$P > 0.10$
Matzies raw scores	41.60	10.75	42.00	10.71	0.750	$P > 0.10$	48.57	11.44	49.14	10.61	2.125	$P > 0.10$
NWLT	41.90	28.03	31.00	21.97	0.279	$0.10 > P > 0.05$	8.00	5.42	7.86	5.05	3.000	$P > 0.10$
AVR	65.70	19.10	54.50	19.82	0.314	$0.10 > P > 0.05$	16.00	11.65	13.57	5.65	0.663	$P > 0.10$
AVRg	42.50	22.62	35.90	19.25	0.556	$P > 0.10$	13.57	9.62	11.86	4.41	1.417	$P > 0.10$
VVRg	23.60	11.07	19.90	10.17	0.313	$0.10 > P > 0.05$	11.71	4.75	11.14	2.73	4.875	$P > 0.10$
VDRg	13.30	7.90	13.80	8.53	5.540	$P > 0.10$	11.86	16.85	9.57	9.96	0.587	$P > 0.10$
VDR †	27.20	26.68	30.39	0.345	0.10 > $P > 0.05$	28.25	29.68	18.25	18.62	0.712	$P > 0.10$	
TDRg	24.10	15.63	28.20	14.63	1.057	$P > 0.10$	24.57	25.18	23.14	15.23	9.360	$P > 0.10$

* As the scores involved in these comparisons are correlated, the significances were calculated by means of Sandler's *A*-test. **

† Five dominant and four nondominant patients were tested on this test.

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TABLE 3.—Statistical Analysis of Results: Significance of Mean Differences Between Preoperative and One-Year Postoperative Test Scores

	Dominant Group (N=10)				Nondominant Group (N=7)							
	Preoperative		1 Yr.		Postoperative		1 Yr.					
	Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.				
Wechsler Verbal Scale I. Q.	94.80	13.29	89.20	16.03	0.347	0.10 > P > 0.05	106.00	24.77	112.85	24.82	0.181	0.01 > P > 0.01
Wechsler Performance Scale I. Q.	102.00	12.79	102.00	13.15	0.0	P > 0.10	101.00	26.01	111.43	21.89	0.233	0.05 > P > 0.02
Wechsler Full-Scale I. Q.	98.20	13.50	95.20	14.87	1.035	P > 0.10	103.43	27.29	113.14	24.07	0.190	0.01 > P > 0.01
Mill-Hill raw scores	39.70	11.67	37.60	10.51	0.769	P > 0.10	50.14	24.96	52.00	23.14	0.337	0.10 > P > 0.05
Matrices raw scores	40.20	11.40	42.00	10.71	0.457	P > 0.10	46.43	11.34	49.14	10.61	0.279	0.05 > P > 0.02
NWLT	9.40	3.34	31.00	21.57	0.180	0.02 > P > 0.01	9.57	8.39	7.86	5.05	0.611	P > 0.10
AVR	20.80	12.30	54.50	19.82	0.134	P > 0.001	19.57	16.83	13.57	5.65	1.034	P > 0.10
AVRg	17.00	6.68	35.90	19.25	0.171	0.01 > P > 0.001	14.85	10.38	11.86	4.41	0.682	P > 0.10
VVRg	18.40	8.38	19.40	10.17	3.960	P > 0.10	11.71	3.15	11.14	2.73	2.875	P > 0.10
VDRg	11.10	6.08	13.80	8.33	0.374	P > 0.10	13.71	19.36	9.57	9.96	0.695	P > 0.10
VDR	20.40	21.12	25.80	30.39	0.676	P > 0.10	26.50	24.84	18.25	18.62	0.557	P > 0.10
TDRg	27.00	15.96	28.20	14.63	5.041	P > 0.10	26.28	24.49	23.14	15.33	1.421	

One dominant case from the preliminary study was tested on AVR and AVR_g four years after the operation; his score on both tests was found to be well outside the pre-operative distributions of the dominant group. Thus, it appears that the auditory verbal learning impairment may persist even longer than one year.

Interrelationships of Some Relevant Factors.—1. The auditory learning tests were intercorrelated preoperatively and one month after operation for the dominant group to determine to what extent they measure this type of learning ability in common for this type of patient. All values were positive, and their magnitudes were either significant or approaching significance (Pearson's product-moment mean $r=0.63$).

2. The correlations between I. Q. measures (Wechsler Full-Scale and Matrices tests) and the auditory learning tests were calculated preoperatively and one month postoperatively to see whether the failure to learn postoperatively depends on intelligence level. All the correlations were low and insignificant (mean $r=0.18$). These findings supported the results of the preliminary study, indicating that this type of learning ability is not significantly related to intelligence level either before or after the operation.

3. Since it was argued that the deficits manifested by the dominant group would be mainly due to dysphasic disturbances and impairment in the auditory modality, one would expect positive correlations between deficits, particularly between deficits on learning tests and on verbal I. Q. tests. The expectations were supported to some extent, and the coefficients were positive, but only three of them attained statistical significance (mean $r=0.37$).

4. In order to determine to what extent nominal dysphasia was related to the deficits, the dominant cases were divided into a group with marked or moderate dysphasia and a group with mild or no dysphasia. The group with a high degree of dysphasia showed greater declines on all tests than the group with a low degree of dysphasia, but

only two *t*-values were significant, i. e., for the Mill Hill test and the NWLT. Also, consistently with expectations, the highly dysphasic group produced the greatest declines on verbal tests. There was practically no difference on AVR_g for the two groups, which finding supported the expectation that the postoperative auditory-learning inability does not depend on nominal dysphasia alone.

5. In order to determine the effect of visual field defects on the Wechsler Performance Scale, all the cases were divided into three groups; Group I, severe defect; Group II, quadrantic defect; Group III, minimal defect. Analysis of variance showed that the greater the amount of visual field defect, the greater the deficit on the Performance Scale ($F=9.40$). In fact, the group with minimal defect produced a slight gain.

6. The age of each patient was correlated with the degree of various deficits and with the amount of recovery in time. All the correlations between age and amount of deficit were positive; however, only three of them attained significance (mean $r=0.33$). Partial-correlation technique failed to establish any relationship between age and the amount of recovery in time (mean $r=0.093$).

7. The extent of the operation (within the reported limits, i. e., 4.5-8 cm.) was not correlated significantly with any test deficits one month after the operation (mean $r=0.21$).

Analysis of variance indicated that the extent of the operation did not determine at all the amount of dysphasic disturbances ($F=0.18$).

As regards the relation of the extent of operation and the amount of visual field defects, analysis of variance indicated that the relationship was neither pronounced nor simple. While it was clear that the less extensive removals produced significantly more minimal defects than the more radical removals, the most extensive operations tended to result in quadrantic defects rather than in severe defects. The mean extent of the operation for the quadrantic-defect

group appeared to be greater than the mean for the severe defect group. Thus, instead of a straight regression line, as suggested by Penfield,²⁵ the findings resulted in a curvilinear relationship. It is possible that such a relationship may be confirmed by a more adequately controlled study and analysis.

Comment and Conclusions

It has been established that this type of operation, when performed on this kind of patient on the nondominant temporal lobe, has no immediate or long-term effect on general intellectual functioning. A similar operation, when performed on the dominant temporal lobe, results in a significant decline on some intelligence measures. Long-term reassessment of this group indicates that some recovery takes place; however, as a group, these patients still tend to function below their preoperative level.

The findings indicate that the dominant group is less efficient on some tests of intelligence, owing to specific disabilities; but their general intelligence is relatively unimpaired if assessed on tests not affected by the specific disabilities. It appears, consistently with Kennedy and Wolf's view,²⁶ that at least this type of dysphasic disorder results in a loss of verbal symbols, leaving the "thought process" unimpaired.

The available data do not permit clear-cut conclusions as to the extent to which particular disabilities are related to the various deficits, nor is it possible to describe more precisely the nature of these deficits. Our data indicate that nominal dysphasia is related to deficits on verbal tests and that this symptom is also related to decreases on the Performance Scale of the Wechsler test. However, it is possible that a high degree of dysphasia always occurs with the auditory impairment, which itself would result in declines on any test involving verbal material. As expected, severe visual field defects are related to the deficits on the Performance Scale.

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Contrary to expectations, the group with operation on the nondominant temporal lobe failed to lower scores on the nonverbal tests. A possible explanation for the discrepancy between our findings and those of Milner¹⁸ is that in her cases the operation extended farther back along the inferior surface of the temporal lobe.

The evidence shows quite clearly that learning ability, as measured by the present tests, remains practically unchanged up to one year following the operation on the nondominant side. The operation on the dominant side results in a severe deficit of auditory learning, which may persist for longer than a year. Individual differences are considerable. There is no reason to suppose that the impairment is due to some uncontrolled factor, and it is clear that the failure to learn after the operation does not depend on intelligence level.

The deficit cannot be accounted for merely in terms of nominal dysphasia. Patients with nominal dysphasia have difficulties in recalling verbal symbols, even though they recognize them. Despite this, they manifest a deficit on a test using the recognition mode of reproduction (AVR_g). Consistent with the nature of nominal dysphasia, the group showing a high degree of this symptom manifests greater mean deficits on NWLT and AVR than the group with a low degree of this symptom. On AVR_g , on the other hand, the mean deficits for the two groups are practically identical. Finally, despite the considerable amount of recovery from the manifest dysphasic disturbances a year after the operation, the auditory-verbal-learning impairment persists.

Further analysis of the nature of the impairment must necessarily be regarded as tentative. The most acceptable view would be that the deficit on the auditory learning tests is mainly related to an impairment of the auditory modality, resulting in a difficulty in the registration and retention of verbal impressions. In our cases this difficulty does not occur obviously to affect

primary hearing, or even perception of simple speech patterns, since there is no impairment on audiographic or on hearing-for-speech tests. It appears that the postulated defect would mainly affect registration and retention of unfamiliar or complex verbal material. In addition, it is possible that the ability to make new associations between verbal impressions is impaired.

It should be pointed out that the patient showing severe impairment copes efficiently with everyday affairs. This, of course, may be due to the specificity of the deficits, which may be overcome by making use of other modalities. Reports by some of the more intelligent patients confirm our analysis of the nature of impairment. Several of them complained of difficulties in following fast conversation and in retaining spoken language. One patient lost his job as a telephone operator.

The findings provide strong support for regional equipotentiality of brain functioning. This particularly applies to the controversial issue regarding the status of learning following brain injury. It is clear that excision of different parts of the brain have different effects on learning.

It cannot be maintained that the defects demonstrated by our battery of tests are the only ones following temporal lobectomy on the dominant side and that they exclusively depend on this area of the brain. However, it appears that the operation on the nondominant side does not result in an impairment of the cognitive functions actually tested in this study.

It would be of importance to investigate further the nature of the auditory impairment. One would like to know whether there is any impairment of the threshold of auditory perception, of simple auditory conditioning, and whether long-term auditory retention would be affected if the material was learned to a criterion. Eventually, it would be desirable to bring the deficit under experimental control and to design a re-training technique for the patients manifesting such gross deficit.

Summary

The aim of the investigation was to confirm the tentative findings of the preliminary study on patients undergoing temporal lobectomy for the relief of focal temporal lobe epilepsy, to define more closely the nature of the deficit, and to assess long-term effects.

Results on a total of 25 subjects, tested before and one month after the operation, are reported; 17 of these were tested one year after the operation. The findings indicate that after the operation on the non-dominant side general intelligence and learning ability remain practically unchanged. A similar operation on the dominant side results in an impairment of specific abilities, leaving general intelligence relatively unimpaired. The most striking deficit manifested by this group is that of the auditory verbal learning ability. The data indicate that this impairment is mainly due to disturbances in the auditory modality (difficulty in the registration and retention of verbal impressions). This disability may persist for even longer than a year. Visual and tactile learning ability remains practically unchanged.

Relationships of various relevant factors are examined and discussed. It appears that neither neurological defects nor psychological deficits are strongly related to the extent of the operation. Also, the age of patients does not seem to determine the amount of psychological deficits nor the degree of recovery from them.

Mr. Murray Falconer, Director of the Guy's-Maudsley Neurosurgical Unit, and Dr. Denis Hill, Consultant Physician to the Maudsley Hospital, provided facilities for this study. Part of the investigation was made possible by a grant from the Research Fund, awarded by the Board of Governors of the Bethlem Royal Hospital and the Maudsley Hospital.

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Radioarsenic in Plasma, Urine, Normal Tissues, and Intracranial Neoplasms

Distribution and Turnover After Intravenous Injection in Man

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Introduction

During the evolution of brain-tumor localization by means of positron-emitting radioactive isotopes over the past four years, a large amount of data on the behavior of inorganic arsenic in man has been accumulated.^{1,2} The experimentally determined distribution and turnover of radioarsenic (As^{74}) in normal tissues, as well as in various intracranial neoplasms from over 100 patients studied, constitute the material of this report.

Methods

A. Preparation and Administration of the Isotope.— As^{74} is produced by deuteron bombardment of germanium powder in the cyclotron. A modification of the separation described by Green and Kafalas³ is now used to obtain carrier-free activity, largely as the trivalent arsenite. In this procedure, the irradiated germanium powder is dissolved in nitrohydrochloric acid (aqua regia) and the germanium driven off as the tetrachloride gas by heating. Hydrobromic acid is added to reduce the arsenic to the trivalent state, and the latter is then extracted in benzene. After it has been taken up in distilled water, the pH is adjusted with NaOH and HCl. The solution is then filtered and autoclaved. It is administered intravenously in a dosage of 2.3 mc/70 kg. body weight. The ratio of As^{74} to As^{75} is much greater than 1, the former usually constituting over 90% of the total. Significant quantities of 26-hour half-life As^{72} are initially present. However, the majority of the determinations were carried out after the contri-

bution of the shorter-lived activity became negligible, and the As^{74} , with its 17.5-day half-life, predominated.

B. Materials.—The sampling may be divided into three groups: 1. Plasma and erythrocytes, urine, and feces were assayed to determine disappearance of arsenic from the intravascular compartment, its rate and per cent of recovery in the urine, and its fecal excretion. 2. Biopsy specimens of normal brain, tumors, muscle, and bone, taken during operation at varying times after radioarsenic injection, were assayed to determine the concentration in these tissues and the significant differences in isotopic uptake between normal brain and neoplastic tissue. The latter constitute the basis for the clinical usefulness of brain-tumor localization by positron-emitting isotopes. 3. Lastly, autopsy material furnished data on the arsenic concentration in the major organs and tissues of the body at different time intervals.

C. Measurement Techniques.—Radioactive arsenic was measured in each biological sample in a standard well counter containing a crystal of thallium-activated sodium iodide associated with a photomultiplier tube and decade scaler. In every series of determinations known standard dilutions of the activity given the patient were counted with the samples. As the physical decay of the samples and that of the standards are equal, the computation of arsenic concentration in the samples reflects only biological processes. Tissue concentrations are expressed as per cent of dose per kilogram or liter of sample normalized to a 70-kg. body weight. Total dose is calculated from the counting rate of the standard times appropriate factors for dilution and administered volume. Arsenic concentrations were calculated in the erythrocytes from the values given by plasma and oxalated whole-blood samples by the relationship, $C_e = C_b - (1 - Ht)C_p/Ht$, where C_e , C_b , and C_p are the concentrations in the erythrocytes, whole blood and plasma, respectively, and Ht is the hematocrit. Urine samples were also assayed for recoverable radioactive arsenic activity. The proportions of trivalent and pentavalent activity were determined by benzene extraction of aliquots of urine strongly

Accepted for publication April 23, 1958.

Neurosurgical Service (Drs. Mealey and Sweet) and the Physics Research Laboratory (Dr. Brownell), Massachusetts General Hospital.

This work has been supported by the Atomic Energy Commission, the National Institutes of Health, and the June Rockwell Levy Fund.

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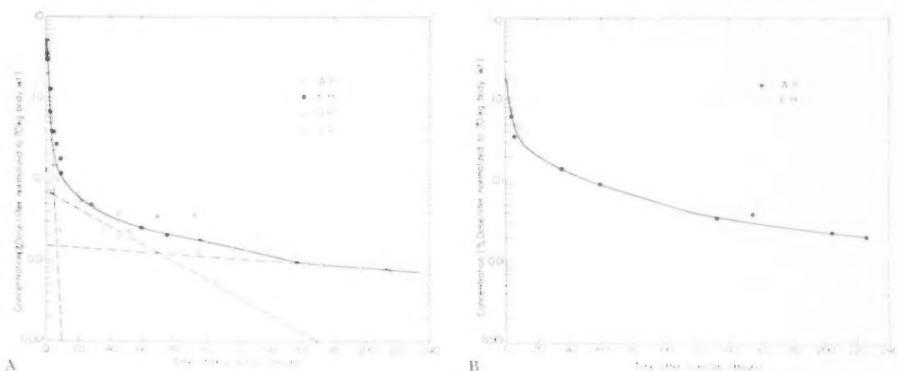


Fig. 1.—*A*, concentration of radioarsenic in the plasma of four subjects as a function of time. Dashed lines 1, 2, and 3 represent postulated exponential components of the experimental curve. *B*, concentration of radioarsenic in the erythrocytes of two patients as a function of time.

acidified with concentrated hydrochloric acid. Arsenite is taken up in the benzene phase, and the arsenate remains in the acid phase. Organ samples were either counted immediately or placed in the Deepfreeze for assay at a later date. Histological controls were obtained from samples of normal brain and tumor prior to assay and before freezing. In either situation, samples were quickly wet-weighed on waxed Celluloid to minimize losses by drying and then rapidly frozen on carbon dioxide snow (Dry Ice) for quantitative transfer into test tubes for counting.³

Results

A. Concentration in Plasma and Erythrocytes and Rate of Excretion in Urine.—The concentration-time course of radioarsenic in the plasma of four patients and the erythrocytes of two patients is shown in Figure 1*A* and *B*. These patients, in relatively normal health, were followed over a period of up to 10 days. The earliest points of the data are taken 15-20 minutes after intravenous injection, and the initial portion of the disappearance of arsenic from the plasma, affected considerably by such factors as mechanical mixing, is not seen. The curves for plasma and erythrocytes are similar in that they decline at comparable rates. Arsenic is seen to concentrate more in the red cells after 10 hours by a factor roughly of 3. The plasma curve appears to have at least three distinct components. There is initially a rapid decline for two or three hours, which then curves into a more gradual ex-

ponential drop until the end of the first week. After this, the disappearance rate is even slower, with a fairly constant slope up to 10 days.

The analysis of disappearance curves of radioisotopes from plasma is usually based on the compartment theory, i.e., the assumption that the labeled substance is distributed in a few relatively discrete and well-mixed compartments interconnected by a limited number of transfer pathways characterized by means of rate constants. For many simple models the disappearance curve of the label from the plasma and its rate of appearance in the urine may be represented by a series of decreasing exponential terms. The hazards of overinterpretation of such data are well known, but it is often convenient to perform such analyses for qualitative interpretation of such data and for convenient reference.

The average plasma concentration curve of Figure 1*A* may be represented to a fair degree of accuracy by three decreasing exponentials:

$$C_p = A_1 e^{-k_1 t} + A_2 e^{-k_2 t} + A_3 e^{-k_3 t}$$

The third component is obtained by fitting a straight line to the semilogarithmic plot at times greater than six days. The values along this line are then subtracted from the observed data at earlier times, and a second straight line is constructed through the resultant data for the time interval greater

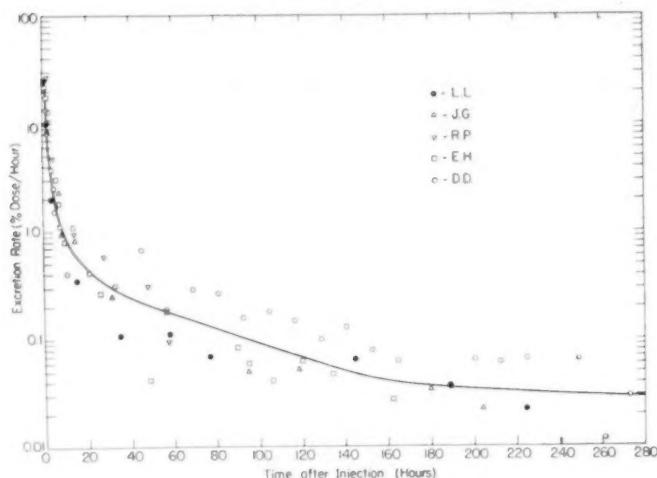


Fig. 2.—Rate of urinary excretion of radioarsenic in five subjects.

than eight hours. The difference between the observed data and the sum of these two curves yields the first component. These three component exponential curves are plotted as dashed lines on Figure 1*A*. The value of the coefficients *A* and the exponential coefficients *B* so found are given below:

$$C_p = 7.0e^{-1.61t} + 0.070e^{-0.007t} + 0.015e^{-0.007t} \text{ % dose/L}$$

Figure 2 illustrates the urinary excretion per hour of radioarsenic in five subjects with normal renal function over a 12-day period. The ordinate values are obtained from the urine-sample concentrations in per cent of dose per liter times the total volume of excretion divided by the collection interval, in hours. This gives the excretion rate in per cent of dose per hour, which is then plotted at the mean time interval. Although the scatter of the data is somewhat greater than in Figure 1*A*, it is seen that the shape of the constructed curve is essentially the same as that of the plasma.

It is of interest to note that the intercept at *t* equals 0 of the plasma curve is 7.09% of dose per liter, which would yield an initial volume of dilution of 100/7.09, or about 14 liters. As this is considerably greater than the plasma volume, which is about 3.5 liters, it must be assumed that the labeled arsenic introduced into the plasma

equilibrated with a second, larger volume, or "space," before the first observations, at 15-20 minutes. The initial "space" is approximately equal to the volume of the extracellular fluid (interstitial fluid, lymph, and plasma). Although quantitative data on arsenic content of extracellular fluid are not available, it may be postulated that the labeled arsenic has been distributed throughout this volume before the initial observations.

The labeled arsenic is seen to leave the plasma at times beyond 15 minutes with a rate constant of 154% per hour. The initial departure rate (for which we have no data) must be much greater. This disappearance may be assumed to result from both diffusion to a second compartment beyond the extracellular fluid and excretion in the urine. The renal clearance rate may be calculated independently by the standard technique of dividing the rate of excretion in per cent of dose per hour by the plasma concentration in per cent of dose per liter for the early portions of both curves (after the first 15 minutes). The renal clearance so obtained is about 3.54 liters of plasma cleared of arsenic by the kidneys per hour. Therefore, the rate of disposal of labeled arsenic from the first observed compartment (extracellular fluid) by the kidneys would be

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3.54% , or about 25% per hour. The diffusion rate of arsenic from the extracellular fluid to the second observed compartment is then $154\% - 25\%$, or 129% per hour. The labeled arsenic is then seen to leave this second postulated compartment at a rate of 2.5% per hour, the major portion of which (in addition to excretion) diffuses into the last-observed compartment. Again, from the plasma rate constant of this last "space," it is seen that removal of the labeled arsenic is very slow, at about 0.3% of that remaining per hour.

B. Recovery of Injected Dose.—Arsenic recovery in the urine is plotted in Figure 3 as the per cent of dose recovered versus time in days, averaged for five patients at the mid-24-hour interval. The curve represents total accumulated activity recovered. The individual recoveries range from 18% to 30% of the injected dose recovered at the end of one hour, to 36% to 56% recovered at the end of four hours, to 57% to 90% of the dose recovered at the end of the ninth day. In one patient who was followed for 18 days, 96.6% of the total injected dose was detected in the urine. The mean time for one-half the injected dose to be meas-

ured in the urine is seen from Figure 3 to be about seven hours.

Arsenic excretion in feces after intravenous injection was studied in two patients. A total of 0.21% of the dose was recovered in one case during the 1st week, and 1.30% of the dose similarly accumulated after 17 days in the second case. No studies of radioarsenic in sputum, perspiration, etc., were carried out.

C. Chemistry of Arsenic Excreted in Urine.—As mentioned previously, radioactive arsenic is administered intravenously as the inorganic trivalent arsenite. Upon standing, however, as a result of atmospheric oxidation, up to 10% of pentavalent arsenate may be present, as determined by repeated benzene extractions in strongly acidified solutions of arsenic activity.

Proportions of arsenite and arsenate present in urine aliquots of five patients were determined by this separate technique. The results are comparable in all, and a representative illustration is shown in Figure 4. Although considerable variation is present, it seems that, generally, there is a decline in that proportion of activity in urine

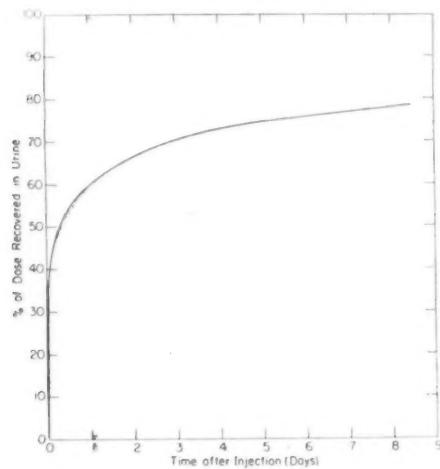


Figure 3

Fig. 3.—Accumulated recovery of radioarsenic in urine (averaged from five subjects in Figure 2).

Fig. 4.—Proportion of radioarsenic recovered in urine of one patient (E. H.) as arsenate and arsenite.

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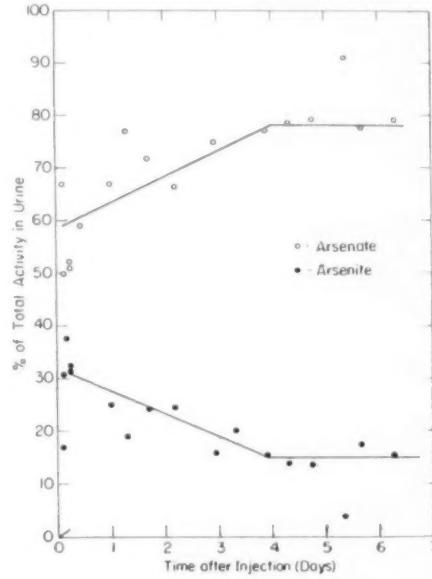


Figure 4

due to arsenite, with a corresponding rise attributable to arsenate, during the first four days after administration of the tracer dose. Then there is a gradual leveling off, until the proportions of each are relatively constant, and over 75% of the recovered activity in the urine is due to the pentavalent arsenate.

D. Biopsy Samples.—Radioactive-arsenic concentrations measured in biopsy samples of normal brain, four categories of intracranial tumors, bony skull, and temporal muscle, taken at various times after injection during operation, are presented in Figures 5 through 9.

For graphic presentation on Figures 5 to 8, because of the magnitude of the scatter inherent in this sampling technique, a method of averaging has been carried out on experimentally determined arsenic concentrations in 140 samples from normal areas of brain in 85 patients. Eight measurements from five additional patients are not included

because of obvious errors in sampling procedure and/or in calculation. The 140 determinations were tabulated in order of increasing time after isotope administration and arranged into 14 consecutive sets of 10 contiguous observations. The average concentration for each of these groups is plotted at the corresponding mean time of the 10 observations. The standard deviations of the mean of the 10 samples are also shown for each group. The data so averaged for brain indicated that arsenic concentration rises to over 0.30% of the dose per kilogram during the first hour after injection, falls during the second hour to mean levels of about 0.25% of the dose per kilogram, and slowly declines thereafter to about 0.16% of the dose per kilogram, at the seventh day.

Arsenic concentrations in biopsy samples of the four tumor types have been individually plotted from experimental measurements on Figures 5 to 8 for comparison

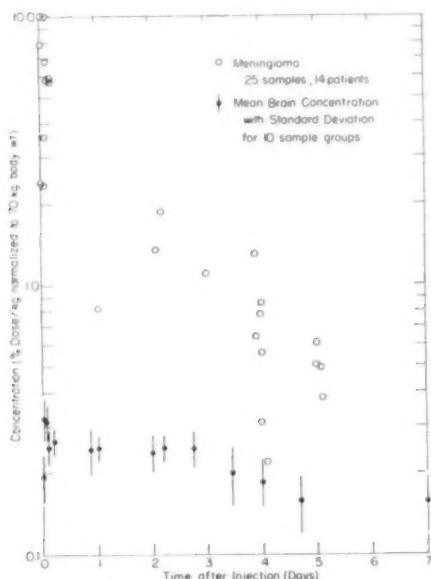


Fig. 5.—Concentration of radioarsenic in biopsy samples of meningiomas obtained at time of operation. Mean concentrations of radioarsenic averaged for 10 contiguous samples of the 140 normal brain samples are also shown, with the standard deviations.

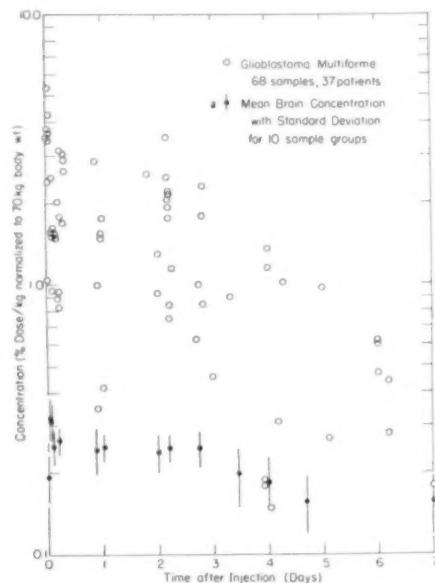


Fig. 6.—Concentration of radioarsenic in biopsy samples of glioblastoma multiforme obtained at time of operation. Mean concentrations in normal brain plotted as in Figure 5.

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with data for normal brain. The wide range at any given time after isotope administration reflects not only differences that generally exist among patients but variations among similar neoplasms and, in some instances, in a single tumor in the same person. In part, these differences are due to the vastly altered physiological conditions present. Locally within the tumor such phenomena as necrosis, infarction, and varying anaplasia, vascularity, and metabolism may induce wide variations in arsenic concentration in different areas of the same tumor. Meningiomas (Fig. 5) as a group take up more arsenic initially, followed in order by glioblastomas (Fig. 6), metastatic carcinomas (Fig. 7), and the slow-growing astrocytomas (Fig. 8). There is a striking decrease in arsenic concentration in the meningiomas after the first four hours, but glioblastomas, in contrast, seem to retain arsenic tracer in significantly higher concentrations for over 48 hours. Concentrations seen in the relatively more differentiated,

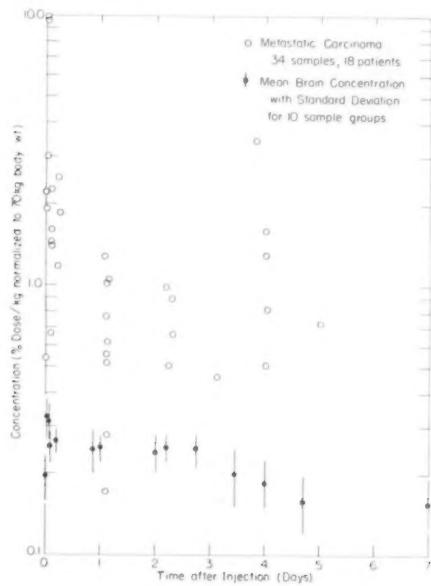


Fig. 7.—Concentration of radioarsenic in biopsy samples of metastatic carcinoma (intracranial) obtained at time of operation. Mean concentrations in normal brain plotted as in Figure 5.

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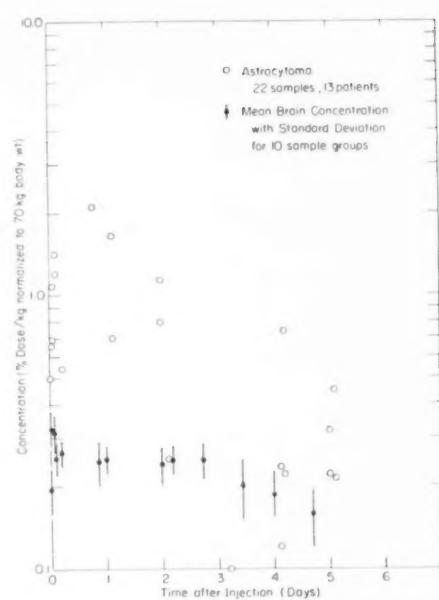


Fig. 8.—Concentration of radioarsenic in biopsy samples of astrocytomas obtained at time of operation. Mean concentrations in normal brain plotted as in Figure 5.

less malignant astrocytomas parallel those obtained in the glioblastomas. Over-all uptake is much lower in the former, however, and this is reflected clinically by the inconstant success experienced in the external localization of the group of slower-growing gliomas by means of positron-scanning.

Arsenic concentrations in 45 biopsy samples of skeletal muscle from 43 patients, and 30 samples of membranous, marrow-free bony skull from 26 patients are illustrated serially in block-graph form in Figure 9. The height read from the ordinate and the center read on the abscissa of each horizontal section in *A* represent, respectively, the average concentration of three samples of bone plotted at the mean time. Similarly, in *B*, each block level represents the average measurement of five muscle samples at the mean time, in days. Although variations exist among samples, as is seen with the values for bone between four and five days, they are not of the magnitude seen with the biopsy data on brain and tumors. Although

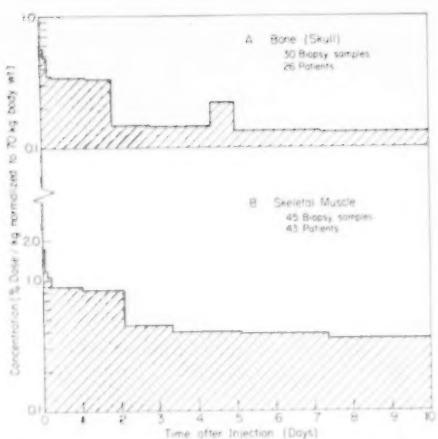


Fig. 9.—*A*, mean concentration of radioarsenic for groups of three contiguous bone samples obtained at time of operation. *B*, mean concentration of radioarsenic for groups of five muscle samples obtained at time of operation.

the arsenic levels in bone are less than one-half those measured in muscle, the general configuration of the concentration-time course of these two tissues is otherwise similar. Measured arsenic activity declines up to four hours fairly rapidly, and then more slowly for the remainder of the time period. Muscle mass is listed as approximately three-sevenths of a "standard man," or 30 kg.⁵ Hence, during the first 48 hours, about 25% of the total administered dose of radioarsenic remains in the muscle, and

after this time, until the end of at least 10 days, about 10% of the dose received persists in this depot.

E. Autopsy Material.—The concentrations of arsenic in various organs and tissues of 11 patients dying of intracranial disease (10 neoplasms) 1 hour to 71 days after receiving the radioactive isotope are tabulated in Table 1, arranged in the order of increasing interval between injection and death. Samples were usually obtained within a few hours of death, at the time of postmortem examination, and were measured for arsenic activity, as previously described. Differences in the organic isotopic levels among patients who survived for about the same length of time are due, in addition to normal variation, to the added factor of individual terminally diseased metabolism. For example, the first patient died shortly after admission, and one hour after radioarsenic injection, of massive infarction of an entire cerebral hemisphere. The next four patients lingered in postoperative comas prior to death, and the remainder experienced similar terminal episodes.

From Table 1 it can be seen that liver, kidney, and muscle are the chief sites for inorganic arsenic throughout the entire series. At one hour, 11% of the given dose is measured in the kidneys, their weight being taken to be about 0.3 kg. Using values

TABLE 1.—Concentration of Radioarsenic in Autopsy Samples *

Case No.	1	2	3	4	5	6	7	8	9	10	11
Time	1 hr.	17 hr.	33 hr.	43 hr.	4 days	7 days	9 days	9½ days	18 days	21 days	71 days
Heart	4.92		1.37	0.62	0.32	0.31	0.25	0.05	0.18		0.043
Aorta			0.50				0.18	0.03			
Spleen	8.35	2.67	5.14	0.76	0.58	0.34	0.35	0.09			
Liver	12.10	6.18	7.35	2.96	1.39	1.13	0.75	0.30	0.83	0.42	0.81
Kidney	36.88	16.71	5.60	2.81	2.10	1.15	1.19	0.23	0.27		0.347
Pancreas	3.76	2.23	1.75	0.61		0.36	0.22	0.082	0.13		0.006
Muscle	0.68	0.79	0.90	0.59			0.484	0.16		0.15	0.071
Bone		1.05	0.77				0.24	0.02	0.14	0.10	
Lung			2.12	0.70	0.31	0.21	0.21	0.10			0.10
Brain	.155	0.77	0.28	0.195	0.13	0.15	0.15	0.05	0.06	0.06	0.011
Scalp		0.32	0.56	0.71		1.77	0.03	0.33	0.34	0.20	
Adrenal	3.78				0.59	0.24	0.39	0.10		0.15	
Testis				1.19	1.14			0.23	0.094		
Intestine								0.42	0.104		
Thyroid				2.31	0.42	0.64	1.01	0.87		0.29	

* Per cent of dose per kilogram of sample normalized to 70 kg. body weight.

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for liver (average weight taken as 1.7 kg.) and kidney found at 71 days, it can similarly be shown that over 1% of the total dose of arsenic originally administered is still present in each of these organs, and about 2% remains in the 30 kg. muscle mass.

With the exceptions of liver, kidney, muscle, and possibly skin, inorganic arsenic seems to exhibit no particularly striking affinity for any one tissue or organ. Concentrations in heart, spleen, pancreas, adrenal, testis, and lung at varying times are roughly comparable. Thyroid concentration may possibly be higher after 48 hours. Brain generally takes up less of the isotope and approximates the concentrations averaged for biopsy material. High concentrations of radioarsenic found in liver and kidney indicate the important role of each in the metabolism of this element. Arsenic concentrations found in the scalp are representative of the skin and appendages. Either progressive accumulation or a very slow rate of removal (compared with other organs) could explain the appreciable concentrations found after one week.

F. Radiation Dose.—The radiation dose rate to any portion of the body may be calculated from the concentration of the radioisotope and its physical properties. The decay scheme of As⁷⁴ is complex, and we use the scheme proposed by Johansson, Caushois, and Siegbahn.⁶ The fractional abundances used in these calculations are the averages of the data mentioned above, measurements of Gleason,⁷ and our own measurements. The average beta energy released per disintegration, \bar{E}_β , is 0.266 mev, and the average gamma energy, E_γ , is 0.812 mev. The F-factor for As⁷⁴ is 4.70 sq. cm. \cdot r/mc \cdot hr.

For a radioisotope uniformly distributed throughout a region of dimensions large compared with the range of the β -rays, the β -dose rate is given by the formula:

$$R_\beta = 51 C \bar{E}_\beta \text{ rad/day}$$

where C is the concentration, in micrograms per gram. Therefore the total dose is

$$D = 13.5 \int_{\infty}^{\infty} C dt \text{ rad}$$

The γ -ray dose is given by the formula:

$$R_\gamma = 0.024 C \rho \bar{g} \text{ rad/day}$$

where ρ is the tissue density and \bar{g} is the average geometrical factor defined as

$$\bar{g} = \int_v \frac{e^{-\mu r}}{r^2} dr$$

The total γ -ray dose is:

$$D_\gamma = 0.024 \rho \bar{g} \int_{\infty}^{\infty} C dt \text{ r}$$

The average whole-body dose may be obtained from the average recovery curve (Fig. 3). The amount remaining corrected for physical decay and divided by the body weight gives an average value of C . Integrating over time gives the value of $\int_{\infty}^{\infty} C dt$.

Because of the rather small variation in concentration throughout the body, the average γ -ray dose, using a \bar{g} of 126 has been assumed to be valid for the γ -ray dose in individual organs. The β -ray dose to various tissues has been calculated from a concentration-time curve obtained from the data of Table 1. The resultant values of radiation dose are given in Table 2.

TABLE 2.—Total Radiation Dose per Millicurie of Radioarsenic (As⁷⁴)

Tissue	β -Dose, Rad	γ -Dose, r	Dose, Total, Rad *
Whole body	0.67	0.71	1.38
Serum	0.35	0.71	1.05
Kidney	4.88	0.71	5.51
Liver	3.52	0.71	4.23

* The rad and roentgen are assumed to be equivalent in soft tissue.

In conventional As⁷⁴ scanning, 2.3 mc. of As⁷⁴ is administered.* The whole-body dose in this case is 3.16 rad, and the kidney dose is 12.7 rad. Approximately one-half the dose is received during the first day. In our opinion, the hazard resulting from this radiation dose is small compared with the potential danger of an intracranial space-taking or vascular lesion. The whole-body

* Standardization is sometimes performed solely on the basis of the beta emission. The fraction of disintegration accompanied by β -rays is 0.65, and the above dose might be expressed as 1.5 mc. of an equivalent pure β -ray emitter.

dose is approximately equal to the 13-week tolerance established for radiation workers in AEC facilities⁹ (3 rem). The kidney dose is approximately equal to the thyroid dose resulting from a 10 μ c. I^{131} tracer in the widely used iodine uptake test. The level is also comparable to the local dose in many diagnostic x-ray procedures, such as chest film with photoentgen survey units (4.4 r). Indeed, repetition of the scanning procedure at intervals greater than three months seems eminently reasonable where clinically indicated.

Comment

Arsenic has been measured in microgram quantities in soil samples,¹⁰ crop plants, and foods,¹¹ as well as cigarettes,¹² and is commonly encountered in industry and medicinals. This abundance in the environment is usually considered the explanation for finding trace amounts of arsenic in normal subjects. Absorption can occur via the lungs, digestive tract, and skin. Arsenic has been chemically assayed in the hair,¹³⁻¹⁵ urine,¹⁶⁻¹⁸ blood,¹⁹ and major organs¹⁷ of healthy persons without known exposure. From studies on autopsy data,²⁰ 0.0000001 of the body weight was given as the estimated arsenic content in a normal subject. This is about 7 mg. per 70 kg. weight.

Radioactive arsenic was administered without addition of chemical carrier. It may be assumed to follow accurately the distribution and reflect the turnover of trace amounts of chemical arsenic in the body. Despite its fairly consistent presence in man, arsenic is not considered an essential trace element. On the contrary, it has been proposed that arsenic is a potentially carcinogenic tissue irritant that the organism strives to remove.²¹ This hypothesis may be used to explain the rapid excretion of radioactive mercury injected as a mercurial diuretic.²²

The biologic action of arsenicals in general is due to the trivalent form, the arsenite.²³ A current view^{24,25} of the mechanism of action of arsenite is that this ion inactivates various enzyme systems by combination with

protein sulfhydryl groups. This inactivation of vital tissue-enzyme systems may be prevented in part by a detoxifying action of circulating amino acid thiols, which bind arsenic as thioarsenite.²⁶

This study has shown that labeled arsenic rapidly equilibrates in the extracellular space and subsequently distributes into a second and third compartment. The equilibration into the third compartment appears complete at six or seven days, and subsequently a slope is observed which probably reflects excretion of the residual arsenic. From the third compartment, about 0.3% of the residual labeled arsenic is released per hour. If 7 mg. is taken as the total body arsenic, the release rate would be about 500 μ g. of arsenic per day. This value falls within the range of chemical assays of arsenic in urine of normal persons.²⁰

Chemical separations show that radioactive arsenic administered intravenously almost entirely as the arsenite is recovered in the urine as a mixture of arsenite and arsenate, with the latter predominating. This suggests oxidation in vivo and preferential excretion of arsenic in the urine as the arsenate. The kidneys may be one site for oxidation of the more toxic trivalent arsenite for excretion as the arsenate. Excretion directly as the arsenite has been postulated to occur in a water-soluble thioarsenite complex with glutathione.²¹ However, in laboratory animals it has been shown that As⁷⁴ injected as the arsenate appears in the urine as both the arsenate and the arsenite in roughly the same ratios as those found here for man.²⁷

The low concentration and relatively slower turnover found for radioactive arsenic in brain are probably not the result of a proportionally lowered chemical concentration as compared with that for other tissues, for trace elements, including arsenic, have been assayed in normal brain at concentrations similar to those in other major organs. When the magnitude of the cerebral blood supply and the active metabolism of the brain are considered, the failure of the labeled arsenic to concentrate more sub-

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stantially in brain may well be ascribed to the operation of the blood-brain barrier. This barrier impedes movement of the labeled arsenic ions from the plasma into the brain. The tracer thus distributes preferentially into other competing compartments, where this barrier is not present.

The appreciable rate of uptake of labeled arsenic by various intracranial tumors may be the result of increased permeability or absence of the limiting blood-brain barrier in the area of neoplasia. This increased uptake does not result solely from absence of the barrier phenomenon, since the concentration of the tracer in these tumors is often greater than that found in other, competing normal tissues, i.e., skeletal muscle. This is probably due to the very active turnover of the arsenic tracer, associated with the increased metabolism and vascularity of neoplastic tissues as compared with normal tissue. Maximal concentrations of labeled arsenic in the four groups of tumors occur shortly after administration of the isotope. Hence it is evident that the optimal tumor/brain ratios are found at these early times. Removal of the labeling isotope from tumor proceeds most rapidly in the meningioma group. The declines in radioactive arsenic concentration seen after injection in the glioblastomas and astrocytomas suggest, in these two groups, as well as in normal brain, that the rate of removal of the arsenic tracer is proportional to its initial rate of uptake. Therefore, at some time after administration of the arsenic tracer the concentration in the tumors should cross the mean concentrations averaged for normal brain. This is seen fairly well in Figure 8, with the astrocytoma group after four days. Because of higher initial concentrations, there is only a suggestion that this holds for the glioblastoma group at times within the first week, seen in Figure 6.

The biopsy and autopsy data on the distribution of radioactive arsenic in the various tissues and organs illustrate the penetration of this element into virtually all of the major tissues of the body. Maximal concentrations are reached soon after injection intrave-

nously. After several days, when a relatively stable state is attained, the inorganic radioarsenic that persists in various tissue depots is only very slowly mobilized and excreted. This is particularly apparent in the autopsy data of Case 11, in which the patient succumbed some 10 weeks after receiving the tracer and in which over 4% of the original dose of arsenic could be still accounted for in the muscle, liver, and kidneys. The high concentrations of radioarsenic common to liver and kidney probably reflect detoxification and excretory processes respectively ascribed to these two organs. Although concentrations per kilogram are not excessively high in muscle, it is important as a major storage site of arsenic. Retention in the various tissue depots, such as liver, kidney, muscle, and skin, provides the basis for the cumulative toxic action commonly seen in chronic arsenical poisoning clinically.

Summary

Concentrations of As⁷⁴ serially assayed in the plasma subsequent to administration of labeled arsenite reflect the complex metabolism of the ion. The concentration curve may be represented as the sum of the three exponential components, the last representing rate of excretion from a tenaciously held small residual pool of arsenic. Activity in the urine is found as both the arsenate and the arsenite.

Serial assays of arsenic concentrations in 149 samples of specific tumor types relative to those of 140 samples of normal human brain have been plotted. Maximal concentrations and optimal ratios in general occur early. The order of decreasing tumor/brain ratios is meningiomas, glioblastomas, metastatic tumors, and astrocytomas.

Radioarsenic (As⁷⁴) is found in all body tissues studied, as determined in 11 patients at autopsies from 1 hour to 71 days after intravenous injection of the isotope. The highest concentrations were in liver and kidney. On the basis of these data, radiation dosage to various tissues resulting from the administration of As⁷⁴ in diagnostic scan-

ning is calculated; it is compared with that incident to other radiographic diagnostic procedures.

A number of the chemical studies on arsenic were performed by Drs. Donald McQueen, Herchell Jick, and Norman Levin. Miss Pauline Montgomery performed many of the sample assays.

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Abstracts from Current Literature

EDITED BY BERNARD J. ALPERS, M.D.

Meninges and Blood Vessels

INTERNAL CAROTID ARTERY THROMBOSIS. B. ROBERTS, G. W. PESKIN, and F. A. WOOD, A. M. A. Arch. Surg. 76:483 (April) 1958.

Partial or complete occlusion of the internal carotid artery by stenosis or thrombosis occurs much more commonly than is generally realized. These conditions should always be considered in the differential diagnosis when a patient of late middle age presents signs and symptoms of a cerebrovascular accident or progressive intracranial disease. As a rule, headaches, paresthesias, focal seizures, or significant aphasia and hemiparesis precede signs of gradually increasing neurologic deficit. A combination of ipsilateral visual loss (due to retinal ischemia) with contralateral hemiparesis is characteristic. The diagnosis is rendered likely when the ipsilateral carotid pulse (palpated at the pharyngeal wall) is absent and blood pressure in the ipsilateral retinal arteries (determined by ophthalmodynamometry) is reduced. Carotid angiography permits one to establish the diagnosis with certainty. The region of the cervical bifurcation and that of the intracranial siphon are the usual sites of vascular obstruction. The treatment must endeavor to restore the circulation and to maintain or improve the collateral blood flow. Occasionally, thrombosis of the cervical portion of the carotid is successfully managed by thromboendarterectomy. In other cases, resection of the occluded segment with subsequent arterial graft is the best method of treatment. Even though these procedures may present no serious technical difficulties, their results are often disappointing because of recurrence or extension of the thrombosis or secondary embolization. The chances of success are best if the patient is operated on early, before the neurologic damage has become irreversible. Little can be accomplished when the intracranial portion of the carotid has been occluded; here, cervical sympathectomy has been recommended. Four illustrative cases are presented; however, only one patient, who was operated upon within 36 hours after the onset of the thrombosis, showed significant neurologic improvement.

LIST, Grand Rapids, Mich.

SPONTANEOUS THROMBOSIS OF THE INTERNAL CAROTID ARTERY IN A 7-YEAR-OLD CHILD. S. L. GOLDSTEIN, and J. P. BURGESS, A. M. A. J. Dis. Child. 95:538 (May) 1958.

Although there are occasional cases of thrombosis of the internal carotid artery in children, the occurrence of such a condition without antecedent trauma or associated systemic disease is rare. Goldstein and Burgess report on a 7-year-old boy who, several hours prior to admission, while playing, suddenly complained of headache and, while getting on his bicycle, fell down. He was unable to get up or to talk. Soon thereafter he became unconscious, and on examination he was found to be semicomatose and cyanotic and to have evidence of right hemiparesis, including the face. Although both pupils reacted to light, the right was larger than its fellow. The Babinski sign was suggestive bilaterally. The blood, urine, and cerebrospinal fluid were normal. The next day he was improved and was cooperative. Seizures of the right upper limb occurred. Two days later he again became comatose, and angiography revealed evidence of blockage of the left internal carotid artery 3.5 cm. above the bifurcation of the common carotid artery. Death occurred, and autopsy revealed that the left internal carotid artery was completely thrombosed, with extension of the thrombus into the anterior and middle cerebral arteries. The intima appeared normal, and there were no obvious arterial or other abnormalities to account for the thrombosis.

SIEKERT, Rochester, Minn.

MENINGITIS CAUSED BY AN UNCLASSIFIED GRAM-NEGATIVE BACTERIUM IN NEWBORN INFANTS. J. A. BRODY, H. MOORE, and E. O. KING, A. M. A. J. Dis. Child. 96:1 (July) 1958.

Bacterial meningitis is not a frequent cause of death in premature or newborn infants. When cases occur, they are sporadic, and the cause is usually one of the coliform bacteria. The authors, who are from the Communicable Disease Center, U. S. Public Health Service, Atlanta, report on two epidemics (1956 and 1957) from South Carolina and Virginia. The

A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY

causative organism has not completely been defined but is a Gram-negative bacillus, recoverable from the spinal fluid. Nineteen infants, mainly premature, were afflicted, and fifteen died. Three of the living are hydrocephalic; the other is normal. The spinal fluid was that of purulent meningitis, and the clinical picture was fairly typical for bacterial meningitis in this age group. Failure to feed, cyanotic episode, bulging fontanel, convulsion, irritability, and failure to gain were common symptoms. The bacillus is generally resistant to antimicrobial agents, although *in vitro* studies suggest it is sensitive to maximum concentrations of erythromycin and carbomycin. The organism has sporadically been sent to this laboratory from a number of states since 1949.

SIEKERT, Rochester, Minn.

ANEURYSMS OF THE ANTERIOR CEREBRAL ARTERY: EVALUATION OF SURGICAL AND "CONSERVATIVE" TREATMENTS. C. H. H. BAUMANN and P. C. BUCY, J. A. M. A. 163:1448 (April 20) 1957.

Baumann and Bucy made a follow-up study of 22 patients with aneurysms of the anterior cerebral system. Seven patients were treated by conservative management. Three patients had surgical decompression and evacuation of a hematoma. One patient had ligation of the common carotid artery in the neck. All but 1 of these 11 patients died. Eleven patients were treated by intracranial clipping of the anterior cerebral artery or trapping of the aneurysm. One of these patients died; one had hemiparesis and aphasia, which were present prior to operation, and the condition of two others is not known. The remaining seven are all well and active. The postoperative follow-up on these patients was four years. On the basis of this study, the authors feel that angiography is a prerequisite to the proper treatment of intracranial hemorrhage resulting from the rupture of an aneurysm. "Conservative" treatment of ruptured intracranial aneurysms carries with it an appalling mortality and is the most dangerous form of management of aneurysms of the anterior cerebral system. Proximal carotid artery ligation cannot be relied upon for cure of aneurysms in this location. Clipping of one anterior cerebral artery may be adequate, but whenever possible the aneurysm should be excluded from the circulation. The anterior cerebral artery on either side may be clipped with relative safety, and this may be done while operating under controlled arterial hypotension.

ALPERS, Philadelphia.

OUTBREAK OF ASEPTIC MENINGITIS CAUSED BY COXSACKIE B5 VIRUS. J. T. SYVERTON, and others, J. A. M. A. 164:2015 (Aug. 31) 1957.

Syverton and his co-workers isolated Coxsackie B5 virus from 61 patients in Minnesota who were ill with aseptic meningitis between July 17 and Nov. 24, 1956. Titers of antibody in 32 patients confirmed injection with Coxsackie B5 virus. On clinical grounds alone, the syndrome exhibited by the 61 patients injected with Coxsackie B5 virus could not be distinguished from nonparalytic disease caused by injection with poliomyelitis virus. Paralytic poliomyelitis was not encountered in rural Minnesota, where patients were suffering from aseptic meningitis, and serological findings showed that these 61 patients were not concomitantly injected with poliomyelitis virus. Results of this study provide further evidence that viral agents other than three known types of poliomyelitis virus may cause clinical illness designated as nonparalytic poliomyelitis until the causative agent is recovered and identified. The number of etiologic agents of aseptic meningitis clinically indistinguishable from nonparalytic poliomyelitis has been found in recent years to include Coxsackie B Types 1-4, ECHO viruses Types 6 and 9, and, possibly, Coxsackie A7 and other viruses.

ALPERS, Philadelphia.

HISTAMINIC CEPHALGIA. B. W. ROBINSON, Medicine 37:161 (May) 1958.

Robinson reports a series of 20 cases of histaminic cephalgia, gathering together for the first time the world literature on the subject and reviewing the clinical picture, etiology, diagnosis, and therapy. The usual age of occurrence is 20 to 50 years, the majority of patients being males. The disease is apparently not familial. The attacks come in clusters. The clusters may recur at the same time each year, the cluster duration averaging about two weeks in this series. The attack frequency averaged two to four per day. The attacks are brief, the duration averaging one to four hours, according to most authors. The attacks are usually nocturnal, and, regardless of when the attacks occur, they tend to recur at the same time each day in any given patient. The pain is referred to as burning, boring, or sometimes throbbing. The pain is usually unilateral, and the side involved is constant. The onset and termination

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of the pain are uniformly described as "sudden." The severity of the pain is a prominent feature. The characteristic nose signs are ipsilateral stuffiness during an attack, with occasional rhinorrhea. The characteristic eye signs are ipsilateral conjunctival injection and increased lacrimation during an attack. The absolute lack of visual symptoms and the relative absence of gastrointestinal symptoms have been commented upon by several authors as important points in differentiating the syndrome from migraine. The disease is one of long symptom-free periods, interrupted periodically by clusters of headaches, which disappear as abruptly and spontaneously as they appear. This fact is of importance in evaluating therapy. The long-term history of the disease is not known. Just as it appears without apparent cause during early or middle adulthood, it may subside after 10 to 20 years in a similar fashion. The histamine provocation test is for all purposes, pathognomonic of the disorder if it is properly interpreted and false-positive results are rigidly excluded. Negative results are much less significant. The efficacy of histamine desensitization, the standard method of treatment since 1939, has recently been doubted on both experimental and theoretical grounds. In this paper, Robinson agrees with this criticism, and states the belief that, in the absence of specific therapy, it is better to treat vasodilation with vasoconstrictors rather than vasodilators. The regimen of the headache has started.

ALPERS, Philadelphia.

ECHO TYPE-9 MENINGITIS IN EAST SCOTLAND. W. M. JAMIESON, M. KERR, and R. G. SOMMerville, Lancet 1:581 (March 15) 1958.

Jamieson and his colleagues report 32 cases of aseptic meningitis. Rising titers of antibody to ECHO virus Type 9 were observed in 22 of the 24 patients examined, and in this group five viruses belonging to ECHO virus Type 9 were isolated from the stools. It is now recognized that the clinical syndrome of aseptic meningitis ("nonparalytic poliomyelitis") has been caused by both the poliomyelitis viruses and the Group B Coxsackie viruses. Recently an association has also been shown with 2 of the 14 serological types of ECHO (enteric cytopathogenic human orphan) virus so far identified. In their group of cases the cerebrospinal fluid was invariably under increased pressure, but usually the increase was slight. The color varied from clear to distinctly turbid. The cell counts varied greatly, and counts approaching 1500 per cubic millimeter were not uncommon even up to the sixth or eighth day of illness. In some cases cell counts, initially low, tended to rise toward the end of the first week, and sometimes this rise was associated with a worsening of the symptoms. Cerebrospinal fluid was usually normal, or approaching normal, by the 14th day. During the first four days of illness there was an excess of polymorphonuclear cells in 8 of the 22 fluids examined. After the fourth day lymphocytes almost invariably predominated. The protein content did not exceed 160 mg. per 100 ml., and in most cases it was less than 100 mg. Sugar contents were within the normal range. The authors suggest that three characteristics are of importance in the clinical diagnosis of aseptic meningitis due to ECHO virus Type 9. 1. There is often a familial association between cases, or evidence from the case history of contact with the disease. 2. The initial severity of the illness is in contrast with the subsequently benign course in all their cases. 3. The various abnormalities in the cerebrospinal fluid, even in some cases with an initial predominantly polymorphonuclear response, return fairly rapidly to normal.

YASKIN, Camden, N. J.

THROMBOSIS OF THE INTERNAL CAROTID ARTERY. E. CLARKE and P. HARRIS, Lancet 1:1085 (May 24) 1958.

Clarke and Harris report five cases of thrombosis of the internal carotid artery simulating an intracranial space-occupying lesion. In four of these cases cerebral neoplasm had been diagnosed, and in one, a cerebral abscess. The authors emphasize that the early symptoms are due to carotid artery insufficiency, and the syndrome of intracranial hypertension is produced by an area of brain softening and surrounding edema which appears eventually. With this etiology the symptoms and signs, as well as the radiographic, cerebrospinal fluid, and electroencephalographic abnormalities, may be identical with those due to a space-occupying lesion. The exact differentiation can be made only by carotid angiography. In three of their cases the patients noted papilledema, which was bilateral. Treatment in these cases, to be effective, must be early, and operation on the arteries seems to be the only hopeful possibility.

YASKIN, Camden, N. J.

Diseases of the Brain

RELATION OF HYPERTHYROIDISM AND PARKINSONISM. E. C. BARTELS and R. R. ROHART, A. M. A. Arch. Int. Med. 101:562 (March) 1958.

After experience with a Parkinsonian patient having hyperthyroidism, the authors undertook a 10-year review of their cases of hyperthyroidism from the standpoint of this association. A relatively low incidence (1 in 270 cases of hyperthyroidism) was noted. It is believed that a theoretical basis for such an association exists in view of recent evidence for a diencephalohypophyseal origin of primary hyperthyroidism. Suggestive also is the similarity of certain symptoms of the two conditions, such as weight and strength loss, heat intolerance with increased sweating and skin flushing, emotional lability, widened palpebral fissures and stare, tachycardia, and tremor. Also cited is the experience of other investigators, who have relieved the Parkinsonism symptoms in euthyroid patients by producing a hypothyroid state through the administration of I¹³¹. The authors recommend serious consideration of this therapeutic approach in the treatment of Parkinsonism patients with elevated or high-normal level of thyroid function.

PARSONS, Montrose, N. Y.

CONCEPT OF EARLY DIAGNOSIS IN STROKES. R. G. SIEKERT and C. H. MILLIKAN, A. M. A. Arch. Int. Med. 101:872 (May) 1958.

The authors stress the early diagnosis of intracerebral vascular insufficiency, as opposed to thrombosis of intracranial vessels with infarction on the basis of the presence of fugitive symptoms suggesting phenomena preliminary to actual occlusion, in contrast to the stepwise progression of the relatively fixed symptomatology which is typical of thrombotic processes. As opposed to the classical methods involving consideration of symptomatology attributable to occlusion or insufficiency of one or another single vascular channel, the authors select the two broad circulatory systems, namely, the basilar and the carotid, for special attention. The points of differentiation enabling the accurate diagnosis of insufficiency of the basilar system include bilateral hemonomous visual field defects; vertigo, especially in the absence of auditory symptomatology; quadriparesis, and bulbar symptomatology. Useful in the diagnosis of insufficiency relevant to the internal carotid system is the presence of ipsilateral amaurosis with decrease in the retinal arterial blood pressure, contralateral motor and sensory defects, aphasia, decreased pulsation of the ipsilateral carotid artery, either in the neck or in the pharynx, and, on occasion, contralateral bruit. The absence of convulsions is stressed. The authors emphasize the importance of the prompt recognition of these premonitory symptoms of vascular insufficiency, inasmuch as they not infrequently presage the development of a major occlusion. If recognized during the preinfarction phase of intermittent insufficiency, various therapeutic steps, such as the use of anticoagulant drugs, may be taken to avoid subsequent thrombosis with resultant irreversible brain damage.

PARSONS, Montrose, N. Y.

ATYPICAL HEAT STROKE, WITH HYPERNATREMIA, ACUTE RENAL FAILURE, AND FULMINATING POTASSIUM INTOXICATION. C. R. BAXTER and P. E. TESCHAN, A. M. A. Arch. Int. Med. 101:1040 (June) 1958.

Baxter and Teschan call attention to three patients sustaining fatal heat stroke in which the clinical picture in its earlier stages was dominated by mental changes and the classical severe hyperthermia was absent. Symptoms included obfuscation, disorientation, irrationality, and combativeness, suggesting psychiatric illness, and in no instance did the temperature exceed 103 F until later in the course of the illness. Initial treatment for heat cramps was given; salt tablets administered resulted in sodium excess without relieving symptoms. Subsequent treatment was directed toward the lowering of body temperature and correcting shock by rapidly reconstituting the volume of circulating blood (electrolyte and blood transfusions) and by decreasing the volume of the vascular tree (levarterenol). The two- to three-day course was subsequently characterized by severe hyperthermia, occurring with circulatory failure, anuria, hypernatremia, metabolic acidosis, and gradually increasing hyperkalemia. Acute tubular necrosis was the salient autopsy finding in each case. The authors attribute the hypernatremia to the administration of large quantities of saline against a background of prolonged sweating of hypotonic fluid, plus oliguria. The hypernatremia, in turn, resulted in an extracellular fluid of sufficient hypertonicity to maintain its volume over a relatively protracted period, thus masking the heat stroke syndrome by delaying shock and collapse.

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The hypernatremia also might have similarly contributed to development of central nervous system symptoms by producing cerebral edema. Finally, the authors state the belief that under conditions of metabolic acidosis the increased extracellular sodium ions exchange with intracellular potassium, producing hyperkalemia, with resulting fatal myocardial intoxication. The authors caution against the use of blood, which may increase peripheral sludging, as well as levarterenol, especially in the presence of hyperthermia, since the ensuing peripheral vasoconstriction impedes heat loss. Finally, early recognition of the diagnostic significance of psychiatric changes in the atypical heat stroke syndrome is preliminary to the institution of prompt corrective measures critical to the successful management of the condition.

PARSONS, Montrose, N. Y.

IDIOPATHIC HYPOPARATHYROIDISM. W. SAPHIR and A. CAHUE, A. M. A. Arch. Int. Med. 101:1143 (June) 1958.

A 57-year-old woman with idiopathic hypoparathyroidism presented hypocalcemia with tetany and an abnormal electroencephalogram suggestive of epilepsy. She was successfully treated with calcium and vitamin D. Although the patient experienced no convulsive seizures, the authors indicate that a number of such patients with typical electroencephalographic abnormalities may develop convulsions should they become hypocalcemic for any reason. No generalization as to the effect of treatment on EEG abnormality can be made. In view of the fact that over 50% of patients with idiopathic hypoparathyroidism develop seizures, that the diagnosis is rarely made, and that the effective treatment is available, the authors recommend that a high degree of suspicion for this condition be entertained in the differential diagnosis of epileptic seizures.

PARSONS, Montrose, N. Y.

STUDIES IN MYASTHENIA GRAVIS: REVIEW OF 282 CASES AT THE MOUNT SINAI HOSPITAL, NEW YORK CITY. K. E. OSSERMAN, P. KORNFELD, E. COHEN, G. GENKINS, H. MENDELSON, H. GOLDBERG, H. WINDSLEY and L. I. KAPLAN, A. M. A. Arch. Int. Med. 102:72 (July) 1958.

The authors report a statistical review of findings and results in a series of 282 patients studied at the Myasthenia Gravis Clinic of the Mount Sinai Hospital, New York. As had previously been reported, females predominate 2:1, and in the severer cases the ratio is still higher. Females are afflicted at a younger age than males (peak 20-30, as compared with 40-50, years of age). The acute, fulminating form is more frequent in males, and in such instances there was found to be a higher incidence of thymoma. These patients responded less satisfactorily to therapy. Extraocular motor palsies, especially ptosis, were the most frequent findings, occurring at some time in about 75% of patients and constituting the earliest symptom in over 50%. Over 25% of patients having symptoms confined to ocular muscles for two or more years experienced subsequent spread of involvement to other areas, in contrast to what has previously been reported. Other bulbar muscles were first involved in about one fourth of cases, and limb involvement occurred in 50%. Almost one-third experienced respiratory difficulty at some time in the course; only 10%-15% had this as the initial feature. About one-fourth had remission, usually within the first two years of the onset of the disease and without relationship to therapy. Both myasthenic and cholinergic crises occurred in the ratio of 3:1 in about 20% of patients, and also within the first two years. There was a 13% mortality directly attributable to myasthenia. Thymoma was demonstrable by x-ray in 10%, and cases with thymoma tended to show a higher percentage of EKG abnormalities suggestive of myocardial involvement (especially in young Negro males, in whom autopsy findings included myocardial necrosis with secondary inflammatory reactions). The authors propose a classification of pediatric, consisting of neonatal and juvenile types, and adult myasthenia, with five subtypes, the first two to be graded on the basis of initial involvement (localized nonprogressive; generalized progressive), the third and fourth to be based on course (rapid; and slow, then rapid), and the fifth, on outcome (death). Treatment is considered from the standpoint of drugs and surgery. Under drug therapy about 65% improve, 20% remain unchanged, and the rest die. Three drugs are mentioned, and pyridostigmine (Mestinon) is regarded as the drug of choice, although various combinations are indicated in special instances. The selection of drug and adjustment of dosage are achieved by clinical or edrophonium evaluations. Thymectomy is deemed indicated in premenopausal women who have had myasthenia gravis for less than five years and in those whose myasthenia is not well controlled.

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with drug therapy, since thymectomy facilitates regulation by drug therapy. It is to be regretted that no statistics regarding the results of thymectomy were included in the report.

PARSONS, Montrose, N. Y.

LEAKAGE OF SPINAL FLUID INTO UPPER LID FOLLOWING TRAUMA. B. BAGOLINI, A. M. A. Arch. Ophth. 57:454 (March) 1957.

Bagolini reports the unusual case of a 9-month-old baby admitted as an emergency 20 minutes after an automobile accident. The child had a fracture of the right parietal bone with contusion and hematoma of the upper lid of the left eye, slight subconjunctival hemorrhage, and a dilated left pupil, which did not react to light. The child was kept under careful neurologic observation. The progress of the case made a craniotomy imperative, as aspiration of the lid hematoma had shown the presence of cerebrospinal fluid in the lid. The cranial exploration showed a fracture of the superior orbital plate with downward displacement, and with laceration of the meninges, as well as of the superficial surface of the frontal lobe. The cerebrospinal fluid was leaking through the meningeal tear. The postoperative course was uncomplicated, and the patient made a satisfactory recovery except for continuation of paralysis of the superior division of the third nerve. The temporary disturbance in the left eye disappeared entirely.

SPAETH, Philadelphia.

VISUAL FIELD DEFECTS DUE TO OPTIC NERVE COMPRESSION BY MASS LESIONS. M. CHAMLIN, A. M. A. Arch. Ophth. 58:37 (July) 1957.

Chamlin reports on the visual field defects in sphenoid ridge meningioma, olfactory groove meningioma, orbital tumor, and frontal meningioma. The truly discrete "central" scotoma which occurs as a result of mass compression of the optic nerve is probably not nearly as frequent as the literature seems to imply. Mass compression of an optic nerve well in front of the chiasm causes a peripheral defect in the visual field, with accompanying or subsequent central involvement as a direct extension of the peripheral defect. The early temporal field defects found in contralateral involvement from sphenoid ridge meningiomas serve as a basis for estimating rate of growth and extension of a tumor from the opposite side. The clinical importance of such early temporal defect is twofold: (a) It helps to establish a diagnosis of mass lesion, as differentiated from optic neuritis; (b) it furnishes criteria which would help the neurosurgeon to decide whether or not to risk surgery on an elderly patient or on one in whom the surgical risk is great. It appears from the evidence presented that the visual field defects due to mass compression of the optic nerve may be explained on the simple mechanical basis of direct pressure transmitted through the nerve trunk, involving outer and inner fields, without invoking any special vulnerability of the macular fibers—at least, not to pressure. One cannot rely on visual fields alone in differentiating between mass compression and retrobulbar neuritis. All other clinical modalities must be utilized, particularly a thorough, painstaking history, always a reliable tool in making a differential diagnosis.

SPAETH, Philadelphia.

BILATERAL PAPILLEDEMA IN OTHERWISE WELL PATIENTS. M. W. FRIEDMAN, A. M. A. Arch. Ophth. 58:59 (July) 1957.

Friedman states that bilateral papilledema in otherwise well patients is not uncommon. He reports a case in a 26-year-old white woman who made a complete recovery, except for residual fundus scarring, nine months after the onset of symptoms. He suggests that the syndrome is self-limited, that its outcome is generally favorable, and that, should vision be endangered, operative intervention is indicated.

SPAETH, Philadelphia.

RETINITIS PIGMENTOSA, ACANTHOCYTOSIS, AND HEREDODEGENERATIVE NEUROMUSCULAR DISEASE. A. L. KORNZWEIG and F. A. BASSIN, A. M. A. Arch. Ophth. 58:183 (Aug.) 1957.

Kornzweig and Bassin report a case of an atypical type of retinitis pigmentosa with progressive neuropathy, and with a hitherto undescribed abnormality of the red blood cells. The pigmentary degeneration was marked, with fields contracted for white in the right eye and the left eye appearing normal. The neuropathy manifested itself by inability to arise with ease from a reclining position. The gait was waddling and unsteady. There were marked lordosis and prominence of the abdomen, wasting of the muscles around the shoulder girdle and upper and lower extremities, and weakness of the muscles of all extremities and the

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trunk and neck. All the deep reflexes were absent and could not be obtained with reinforcement. The patient had a positive Romberg sign, ataxia in the performance of the heel-to-knee test, and some ataxia in the finger-to-nose test. Dysdiadochokinesia was evident in both hands. Vibration sense was very much diminished to absent in all four extremities. This loss was most marked distally and below the iliac crests. Position sense was impaired in the toes. There was a glove-and-stockings type of hypesthesia. The speech was nasal. Hearing was slightly defective for high tones. The blood picture showed unusual abnormalities in shape, and to some extent in size, of great numbers of the red cells. The cells had a crenated appearance, but of such a degree that they took on bizarre shapes, simulating small beetles, crabs, and turtles. Others were star-shaped. Some of the red cells resembled spherocytes from which buds or pseudopods were protruding. This is the third reported case of this rare hereditary disturbance.

SPAETH, Philadelphia.

PARACENTRAL HOMONYMOUS HEMIANOPIC SCOTOMA. J. DESSOFF, A. M. A. Arch. Ophthalm. 58:452 (Sept.) 1957.

This type of field defect is rare, only 15 such cases having been reported in the literature. Four features characterize this symptom complex: (1) reading defects of various types, depending upon whether the defect is to the right or to the left; (2) sparing of the macula; (3) congruent paracentral homonymous scotomas close to, but not involving, the macula, with normal peripheral fields of vision, and (4) normal optic nerves. The case reported by Dessoff was under observation for two years without change in the scotomas. The exact location of the lesion is not certain. The author assumes it to be in the calcarine fissure of the occipital lobe or in the optic radiation. Sudden inability to read in the presence of normal fundi, normal visual acuity, and normal peripheral fields should make one suspicious of this syndrome.

SPAETH, Philadelphia.

OCULAR MANIFESTATIONS OF SICKLE-CELL DISEASE. G. GOODMAN, L. VON SALLMANN, and M. G. HOLLAND, A. M. A. Arch. Ophthalm. 58:655 (Nov.) 1957.

Sickle-cell disease is manifested as an acute or a chronic obstructive vascular disease in Negroes or in Caucasians of Mediterranean origin. Renal and ocular pathology is frequently associated. The fundus changes include the following: retinitis proliferans; aneurysmal vascular dilatations; arborizing vascular networks; focal constriction; dilatation; sheathing and obstruction of arterioles and venules; development of chalk-white vessels, owing to changes in intravascular contents; preretinal hemorrhages, which closely simulate retinal tears, and vitreous and retinal hemorrhages. Vascular changes are also noted on the optic disk and bulbar conjunctiva. Histologic findings in one patient with sickle-cell retinopathy were retinal and vitreous hemorrhage, retinal gliosis blending with a preretinal fibrous membrane, extensive new-vessel formation, obliterated vessels, perivenous lymphocytic cuffing, and sickle cells intravascularly and in the areas of hemorrhage.

SPAETH, Philadelphia.

SPRAL VISUAL FIELDS: STATISTICAL ANALYSIS OF 18 CASES FOUND IN A SURVEY OF 800 UNSELECTED EYE PATIENTS AT A STATE MEDICAL CENTER. T. F. SCHLAEGEL JR., A. M. A. Arch. Ophthalm. 58:18 (Jan.) 1958.

This paper is based upon a statistical analysis of 18 cases of spiral visual fields found in a survey of 800 unselected eye patients. Of these 18 patients, 13 had bilateral spiral fields; 3 had a tubular field in one eye and a spiral field in the other eye. The cases are classified as mild, moderate, and severe. Among clinic patients, the severe type of spiral fields was the commonest, whereas with private patients the mild type was most commonly observed. Spiral fields are frequently known as fatigue, or neurasthenic fields. Many authors include them in their discussion of hysteria; others deny any element of retinal fatigue and believe it is necessary to assume a central origin for such fields. If fatigue is active, it would appear to be mental or emotional, rather than physical. The author calls attention to the close relationship which exists between tubular and spiral fields. They can change from one to the other or from one to the normal, or can be combined with a spiral field in one eye and a tubular field in the other. The author felt that the usual progression is for spiral fields to appear first and to pass through the tubular type to the normal.

SPAETH, Philadelphia.

PERMANENT INCREASED INTRACRANIAL PRESSURE FOLLOWING UNILATERAL RADICAL NECK DISSECTION. H. M. MORFIT and H. CLEVELAND JR., A. M. A. Arch. Surg. 76:713 (May) 1958.

The operation of radical neck dissection, which is now widely used for the removal of metastatic cervical cancer, necessitates resection of the internal jugular vein. Unilateral removal of this venous system may produce a temporary rise of intracranial pressure, especially when drainage by collateral vessels is inadequate, but so far no instances of persistent elevation of intracranial pressure have been recorded. The authors report two cases in which unilateral neck dissection caused a prolonged and severe rise of intracranial pressure, with imminent blindness from chronic papilledema. The possibility that the rise in intracranial pressure was the result of either an intracranial metastasis or of a nonrelated primary brain tumor was ruled out by appropriate tests and a long follow-up observation (five years in one case; eight months in the other). Signs and symptoms of increased intracranial pressure subsided in both patients after subtemporal decompression.

LIST, Grand Rapids, Mich.

ELECTROENCEPHALOGRAPHY IN SUBDURAL HEMATOMA IN INFANTS. M. STREIFLER, E. FREUNDLICH, and A. J. BELLER, A. M. A. Arch. J. Dis. Child. 95:25 (Jan.) 1958.

A very high percentage of infants with subdural hematoma and effusion have an abnormal electroencephalogram. Of 14 infants in this series of patients with such lesions, surgically verified, 13 showed abnormalities. These changes consisted of slowing with "flattening" in 11 patients and of only diffuse slowing in 2. The authors believe this simple and harmless procedure is of great aid in the diagnosis of this condition.

SIEKERT, Rochester, Minn.

"SLEEPING FIT" CAUSED BY EXCRUCIATING PAIN IN AN INFANT. I. F. BURTON and A. J. DERBYSHIRE, A. M. A. J. Dis. Child. 95:258 (March) 1958.

"Sleeping fit," apparently first noted by Davidson in 1955, is a particular type of convulsion for which no etiology has been determined and during which the EEG reveals a fast pattern of generalized steady rhythm in the 16-per-second range. The case is reported of a one-year-old boy who awoke suddenly and began to scream and writhe in a complete frenzy for an hour, until he fell asleep. He became unresponsive to all stimuli. Examination revealed no other abnormalities except secondary glaucoma in the left eye. (The patient had been known to have retrobulbar fibroplasia.) The spinal fluid was normal. The electroencephalogram showed some spindles of 12-per-second waves and scattered 3- to 5-per-second waves, characteristic of sleep. In addition, there was a constant overlay or admixture with fast waves, 15- to 18-per second at 40μ v. to 50μ v., strongest in the left frontal leads. The left eye was removed, and within a few hours the boy was completely normal. The EEG three days after surgery was normal. It is suggested that there is a possible relationship of this state of "sleeping fit" and reaction to physical pain.

SIEKERT, Rochester, Minn.

ENCEPHALITIS COMPLICATING ATTENUATED RUBEOLA. H. D. RILEY, A. M. A. J. Dis. Child. 95:270 (March) 1958.

It is extremely rare for encephalitis to occur after measles attenuated by γ -globulin. Two cases are recorded, in one of which necropsy was performed, probably the first so studied. Three weeks prior to admission the sibling of this 8-year-old boy developed measles. The patient received a "preventive dose" of γ -globulin the next day and was well for two weeks, when headache, fever, and rash occurred. He was well within two days. The day before admission headache, somnolence, vomiting, and unusual behavior occurred. He was feverish, soon semicomatoso, and had a stiff neck. The spinal fluid contained 170 leukocytes per cubic millimeter; sugar, 55 mg/100 ml.; protein, 77 mg/100 ml. Cultures were negative. His condition was critical for most of the time until he died, some five weeks later. He developed papilledema, arterial hypertension, and convulsive movements. He was fed by an indwelling polyethylene gastric tube. At times blood-tinged material was obtained from this tube. Purulent material was obtained at thoracentesis, although at no time was a rent in the esophagus demonstrated by the esophagrams. Examination revealed purulent material in the pleural cavity, a rent in the lower end of the esophagus, aspiration pneumonitis, and coffee-ground material in the stomach. The brain weighed 1540 gm. and appeared normal on cut section after fixation. Microscopic examination of the brain revealed perivascular demyelinating lesions, apparently in various stages of development. Early lesions showed slight lymphocytic infiltration.

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tion, astrocytic proliferation, and break up of the myelin around small veins. Later lesions contained numerous round cells and lipid-laden macrophages and fat-filled vacuoles in the white matter. Comments concerning measles encephalitis and neurologic lesions producing gastrointestinal ulceration.

SIEKERT, Rochester, Minn.

RELATIONSHIP OF LITTLE'S DISEASE TO PREMATURE BIRTH. J. A. CHURCHILL, A. M. A. J. Dis. Child. 96:32 (July) 1958.

Churchill analyzed a group of children with Little's disease (cerebral spastic infantile paralysis). All subjects were characterized by varying degrees of bilateral impairment of motility of the extremities and trunk and manifested a bilateral Babinski sign, hyperactive muscle stretch reflexes, increased (usually) or decreased muscular tonus, reduced motility of extremities and trunk, and onset of walking later than 14 months of age. The group was divided into cases with only the above-listed abnormalities (simple spastic diplegia) and cases with the above plus one or more of the following additional abnormalities: convulsive seizures, I. Q. less than 70, athetotic or ataxic movements, positive tonic neck reaction, definite asymmetry of extremity function, greater impairment of the upper than of the lower limbs, and hypotonicity of musculature (complex diplegia). Simple spastic diplegia was found to correlate significantly with low birth weight, while complex diplegia exhibited no significant correlation with low birth weight.

SIEKERT, Rochester, Minn.

TRICHINOSIS INVOLVING THE CENTRAL NERVOUS SYSTEM. L. E. MELTZER and A. A. BOCKMAN, J. A. M. A. 164:1566 (Aug. 3) 1957.

Trichinosis commonly involves the central nervous system. Such involvement may produce either nonspecific neurological signs (headaches, neck stiffness, and decreased deep tendon reflexes) or actual focal cerebral damage, which may be protean in type. Meltzer and Bockman present a case of clearly defined focal cerebral damage due to *Trichinella spiralis* in a 43-year-old man. The neurological complications were definite and included muscle group weaknesses, pyramidal tract signs, aphasia, and altered reflexes. Within 24 hours after treatment with corticotropin and cortisone was initiated, the patient, who had been in a toxic condition and acutely ill, showed marked improvement. The patient recovered completely and was discharged 16 days after admission. The rapidity of disappearance of the neurological deficits would imply that the steroid effect is more likely related to the control of allergic, toxic, or antigen-antibody reactions than to the anti-inflammatory ability of the steroids. The prompt treatment with steroids would appear to be related to the reversibility of the neurological changes in this case. Such changes are often permanent. In this case no sequelae were demonstrated. The authors feel that the dramatic clinical improvement after steroid therapy is in some way related to an antigen-antibody response and that the use of steroid therapy early in the course of the disease is indicated.

ALPERS, Philadelphia.

PROGNOSIS IN POST-TRAUMATIC EPILEPSY. A. E. WALKER, J. A. M. A. 164:1636 (Aug. 10) 1957.

Walker presents the findings on a series of 244 patients with post-traumatic epilepsy who have been followed for 10 years after the occurrence of their head injuries. In patients with post-traumatic epilepsy, mortality and morbidity rates are higher in the first 10 years after their injury than rates in normal persons. The work status of men with post-traumatic epilepsy appears to correlate more closely with intelligence than with frequency of seizures or the neurological deficit. With the therapy in vogue a decade ago, more than a third of this group of patients with post-traumatic epilepsy were free of attacks from the 5th to the 10th year after injury. This freedom from attacks is not necessarily related to the anticonvulsive medication, for more than half of the men were taking no drugs. Favorable prognostic factors were found to be early cessation of attacks, low frequency of attacks, and, strangely, severe neurological deficit. The cases in which seizures developed early in this series did not seem to be more likely to regress than the ones in which they developed late. Improvement was manifested by elimination of attacks or by a shift from major to minor episodes. In evaluating the disability of a patient, after the occurrence of a head injury, the total picture must be examined, for the disturbance is more than the sum of hemiplegia and epilepsy. Even if post-traumatic seizures do develop, it should be understood that they do not forecast recurrent convulsive attacks.

ALPERS, Philadelphia.

A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY

Etiology of the Transient Cerebral Stroke. S. F. Rothenberg and E. Corday, J. A. M. A. 164:2005 (Aug. 31) 1957.

The etiology of sudden, transient focal cerebral vascular disturbances has been the subject of considerable controversy. Such disorders include hemiplegia, monoplegia, hemianesthesia, aphasia, and visual disturbances. They occur suddenly and often disappear rapidly, sometimes within a few minutes. In the absence of other obvious causes of these attacks, it has been convenient in the past to attribute them to cerebral angospasm. Using rhesus monkeys, whose pial vessels are similar to those of man, Rothenberg and Corday outline experiments performed to clarify the etiology of these transient cerebral strokes. The results of the experimental studies suggest that it is unlikely that cerebral angospasm can occur, but, rather, indicate that the transient cerebral stroke is due to cerebral thrombosis, embolism, hemorrhage, or vascular insufficiency. Cerebral vascular insufficiency is due either to cerebral vascular narrowing or to an occlusion in the presence of systemic hypotension. Prompt correction of the condition causing the hypotensive state in cerebral vascular insufficiency will prevent cerebral damage.

ALPERS, Philadelphia.

Incidence of Disseminated Lupus Erythematosus. O. Svaborg and L. Sölvell, J. A. M. A. 165:1126 (Nov. 2) 1957.

Svaborg and Sölvell have compared the incidence of disseminated lupus erythematosus in a Swedish city during three two-year periods (1938-1939, 1948-1949, and 1954-1955). The case records of all patients with nephritis, fever of unknown origin, sepsis, uncertain diagnosis, and diseases of the heart, blood vessels, joints, and skin were reviewed. The suspected cases so found were all followed up, and the diagnosis was verified in 24 cases by data from re-examination, records of later hospitalization, or autopsy. The number of cases (18) during the third period was six times as great as that during the first (3) and the second (3) periods. This is not accounted for by the increases in the population of the city or by any change in diagnostic criteria. This would seem to indicate a real increase of statistical significance in the incidence of disseminated lupus erythematosus.

ALPERS, Philadelphia.

Diagnosis and Treatment of Facial Pain. G. W. Smith, J. A. M. A. 166:857 (Feb. 22) 1958.

Facial pain, which is sometimes extremely severe, may be caused by intracranial or extracranial conditions. The latter include dental disease, tumors or injected cysts of the mandible, disturbances about the temporomandibular joint, lesions involving nasal accessory sinuses and other paranasal structures, elongated styloid processes, nasopharyngeal tumors, tumors involving the trigeminal ganglion and nerve, acoustic neurinomas or cerebellopontine-angle meningiomas, and aneurysms or anomalies of certain arteries. The best-known clinical syndrome marked by facial pain is trigeminal neuralgia. Treatment by root section generally gives relief of pain, but the price that patients pay for complete relief is total anesthesia in the corresponding area. Smith describes a medical treatment that takes advantage of the unusual neurotropic action of stilbamidine isethionate. Injected intravenously, this drug produces a trigeminal neuropathy consisting of hypesthesia and paresthesia, but no motor paralysis. The paresthesias are troublesome in about 20% of the cases but are usually self-limited. The second disadvantage of this form of therapy is that the effect is a delayed neuropathy and the patients may not obtain immediate relief with the use of the drug; instead, the relief may occur anywhere between the 1st and the 14th week. It is necessary to give seven or eight booster injections of the drug every two years, depending on the amount given in the initial course of treatment. Patients have been treated with the oral form of stilbamidine isethionate with good results and without the production of paresthesias of the face. A critical analysis of the therapeutic results in a series on the oral form of the medication is in preparation. Since this drug action affects only the fifth nerve, careful differential diagnosis is essential in order to preclude treatment of atypical neuralgias involving the seventh and ninth nerves.

ALPERS, Philadelphia.

Diagnosis, Prognosis, and Rehabilitation in Patients with Aphasia. E. F. Hoerner and B. Horowitz, J. A. M. A. 166:1573 (March 29) 1958.

The aphasic patient presents a complex and difficult problem to all concerned; however, through careful evaluation of his medical, physical, language, social, and personality status, much can be done to help him. Hoerner and Horowitz clarify the methods and benefits of working with aphasic patients within the framework of the general rehabilitation team set-up, with

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emphasis on the language area. The existing aphasia should be considered as a disturbance having four aspects or involving four functions: understanding, talking, reading, and writing. Careful diagnostic tests identify the nature of the impairment and form the basis for establishing a program of therapy. The goals are thought of in terms of basic communication, home adequacy, social acceptability, and vocational adequacy. Early retraining does much to increase the functional language ability of the patient and aids in alienating the depression and anxiety which, in themselves, create havoc with his general language function. The authors have found that those patients who are seen early after the loss of their language ability are better able to adjust and are better motivated than those who delay therapy. Group therapy is applicable in many forms, and it helps to provide multistimuli situations. The families of aphasic patients also need support and guidance. A family group session sometimes helps to bridge the gaps from the rehabilitation center to the sheltered family home, and thence to the world outside.

ALPERS, Philadelphia.

ELECTROENCEPHALOGRAPHIC CORRELATION OF LAUGHING FITS. A. A. WEIL, W. A. NOSIK, and N. DEMMY, Am. J. M. Sc. 235:301 (March) 1958.

The authors report laughing fits in four children, 4 to 11 years of age. The children exhibited sudden episodes of unprovoked, inappropriate, uncontrollable laughter, associated with other ictal phenomena, such as staring attacks and grand mal seizures. They had other defects, such as hyperactivity, aphasic disturbances, psychomotor retardation, and evidence of focal motor disturbances. Electroencephalographic abnormalities consisted of focal temporal slowing, spike-dome variant formations, and diffuse slowing. The disturbances were attributed to a papilloma of the third ventricle, postencephalitis state, and birth trauma. The attacks were modified by anticonvulsant drugs.

BERLIN, Mount Vernon, N. Y.

POLYCYTHEMIA WITH PAPILLEDEMA AND INFRATENTORIAL VASCULAR TUMORS. G. F. STARR, C. F. STOEBEL JR., and T. P. KEARNS, Ann. Int. Med. 48:978 (May) 1958.

The authors studied 106 patients with infratentorial vascular tumors for polycythemia. In 36% hemoglobin values were greater than 16 gm/100 ml. of blood. Eleven of the patients had hemoglobin values greater than 18 gm/100 ml. Papilledema was found in 10 of these 11 patients.

The difficulty in cases of polycythemia and papilledema is to distinguish the neurological complications of polycythemia vera from posterior-fossa lesions with those findings. Phlebotomy usually produces clinical improvement and subsidence in papilledema in the patients with polycythemia vera. Patients with cerebellar vascular tumors should not benefit by this procedure. The vascular tumors of the posterior fossa may produce absolute or relative polycythemia.

AIGNER, Rochester, Minn.

HYPOPHYSAL DUCT TUMORS (CRANIOPHARYNGIOMAS) VERSUS ADAMANTINOMAS. O. HIRSCH, J. Neuropath. & Exper. Neurol. 17:305 (April) 1958.

Hirsch shows by studies in embryonic and histologic development that tumors of the hypophyseal duct have no relation to adamantinoma of the enamel, even though the microscopic picture is identical, since both structures develop from the epithelium of the embryonal oral cavity. Much of the error arose from a paper by Tilney, which apparently erroneously labeled a dental ridge in the neighborhood of the pituitary pouch. As a result of this, the term pituitary adamantinoma is confusing and inaccurate. Hypophyseal-duct tumors, also called craniopharyngiomas, Rathke-pouch tumors, and suprasellar cysts, develop from the squamous epithelial cells which are residual from the pharyngeal membrane in embryonal development of the hypophysal duct or pouch on the floor of the forebrain vesicle.

AIGNER, Rochester, Minn.

A CLINICO-ANATOMIC STUDY OF PERSONALITY AND MOOD DISTURBANCES ASSOCIATED WITH GLIOMAS OF THE CEREBRUM. J. E. RIGGS and C. RUPP, J. Neuropath. & Exper. Neurol. 17: 338 (April) 1958.

On the basis of Papez' concept that emotional function is channeled through a rhinencephalic-hypothalamic mechanism, Riggs and Rupp studied the clinical and anatomic findings in 86 cases of supratentorial gliomatous lesions. Of the group, 40 patients were without mental symptoms on admission and gave no history of recent psychological disorder; 46 presented with disturbances of emotion and behavior as early conspicuous signs. Invasion of the rhinencephalic-

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hypothalamic structures could be demonstrated in 89% of the cases with psychiatric disturbances, while involvement of the same structures was present in only 20% of the patients who were mentally clear. The authors conclude that their findings suggest that the presence or absence of psychiatric symptoms may be dependent on whether or not the "emotional circuits" are involved in the neoplasm.

AIGNER, Rochester, Minn.

CHANGES IN THE NERVOUS SYSTEM IN ACUTE PORPHYRIA. R. HIERONS, *Brain* 80:176 (June 1957).

Hierons reports five cases of acute porphyria with changes in the central nervous system, affecting the peripheral nerves, cerebrum, and spinal cord. In three cases, the peripheral nerves were available, and the principal changes consisted of considerable loss, fragmentation, and swelling of myelin, with macrophage infiltration. Sensory changes were present in two of these cases, and recovery from the complete symmetrical paralysis occurred in one case. Hierons, therefore, favors a disturbance in the metabolism of the nerve fiber as a cause of the pathologic changes, rather than an ischemic or a vascular process, which has been advocated by others. The abnormal blood pyruvate levels in two of the cases would lend supportive evidence to the author's theory. Demyelination of the spinal cord affecting the posterior and lateral columns was present in one case. These changes involved the lumbar region predominantly, with less pronounced changes in the cervical and thoracic cord. These changes have not previously been reported. Well-preserved axons were found in the demyelinated posterior columns, suggestive of a pathologic change damaging the myelin. The cerebral changes consisted of severe vascular lesions in the cortex, which were associated with hypertension and vascular spasms chemically.

MANDEL, Philadelphia.

NEUROLOGICAL COMPLICATIONS OF THE RETICULOSSES. E. C. HUTCHINSON, B. J. LEONARD, C. MAUDSLEY and P. O. YATES, *Brain* 81:75 (March) 1958.

The authors report the occurrence of neurological abnormalities in 45 of 229 patients suffering from various types of reticuloses, which included Hodgkin's granuloma, lymphosarcoma, Brill-Symmers disease, and reticulosarcoma. Spinal cord lesions were the commonest abnormality found in this series, with compression symptoms encountered in 16 of 21 cases. Root pain was a constant feature in each instance, with four patients having compression symptoms as an initial manifestation of the reticuloses. In five patients no evidence of cord compression was noted, but in one of the autopsied cases there were changes consistent with myelomalacia in the peripheral zones of all columns of the spinal cord, particularly in the anterior and lateral columns. Mental changes were found in 17 cases, and they dominated the clinical picture, particularly in the terminal stages of the disease. Abnormalities of the optic fundus occurred in 17 cases, with papilledema without raised intracranial pressure in 2 cases and retinal hemorrhage secondary to thrombocytopenia in 8 cases. Focal intracranial lesions secondary to intra-cerebral hemorrhage were noted in 13 cases, the diagnosis being confirmed by autopsy in 2 cases. Peripheral neuropathy occurred in four cases with clinical manifestations of bilateral weakness, sensory changes, and loss of reflexes. In the autopsied cases, the peripheral nerves revealed a loss of myelin sheaths and axons. Epilepsy was found as a neurological complication in five cases. The authors conclude that the development of neurological abnormalities is not confined to any particular variety of reticuloses and that when neurological signs occur, they may indicate a rapid progression of the disease. The neurological signs were attributed to direct invasion or compression by neoplastic tissue in 21 cases, to spontaneous subarachnoid hemorrhage following thrombocytopenia in 19 cases, and to a degenerative change with elevated blood pyruvate levels in 20 cases.

MANDEL, Philadelphia.

NEUROPSYCHIATRIC SEQUELAE OF LIGHTNING STROKE. D. SHAW and M. E. YORK-MOORE, *Brit. M. J.* 2:1152 (Nov. 16) 1957.

Shaw and York-Moore made a study of the neuropsychiatric sequelae in 28 patients who had been struck by lightning. Headaches and paresthesias were the commonest early after-effects, and the next commonest was transient paralyses of the limbs. Two patients had mild temporary dysphagia. Spinal atrophic paralysis did not occur in any of the authors' cases, although the literature indicates that this is a common sequel of lightning stroke. There were no cases of post-traumatic syndrome or personality change. Only 2 of the 28 patients had prolonged neurotic disabilities, both of whom had a psychopathic background.

ECHOES, New Orleans.

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CEREBROSPINAL FLUID IN VARIOUS DISEASES. M. LOCOGE and J. N. CUMINGS, Brit. M. J. 1:618 (March 15) 1958.

Locoge and Cummings report an analysis of the results obtained from examination of nearly 12,000 cerebrospinal fluid specimens from patients with various neurologic disorders. Among 835 patients with all types of cerebral tumors, the cerebrospinal fluid of 766 (91.7%) showed no increase in cell count. Any increase in cell count occurred in the patients with gliomas. Of the 69 cases showing cell increase, 36 were of patients with cerebral glioma. The protein content was normal in only 242 cases (28.9%). The protein content was elevated in 66.5% of the patients with cerebral glioma and in 69.6% of those with secondary carcinoma; in those with acoustic neurofibroma it was as high as 100%. The other tests showed no noteworthy features. The cell content was normal in 589 of 690 (85.4%) specimens from patients with multiple sclerosis, and only 3 patients had a count above 50 per cubic millimeter. The protein level was 100 mg/100 ml. or lower in 665 cases (96.4%), and only 1.9% had a level higher than 150 mg/100 ml. The result of the Nonne-Apelt test was positive in 138 (20%), and that of the Pandy test, in 280 (40%). The Lange curve was normal, or virtually normal, in 481 (69.7%), and 125 (18.1%) had a pronounced syphilitic curve; 84 (12.2%) had a paretic curve. The Wassermann reaction was invariably negative. In all 41 cases of subacute combined degeneration the cell count was normal. The protein was normal in 20 cases, 100 mg/100 ml. or less in 39 cases, and between 100 and 200 mg/100 ml. in only 2 cases. In 22 cases of diabetic neuritis there was no cell increase; the protein was normal in 6 cases, raised to 100 mg/100 ml. in 19 cases, between 100 and 200 mg/100 ml. in 2 cases, and over 200 mg/100 ml. in only 1 case. In 37 of 75 cases of infective polyneuritis the protein exceeded 100 mg/100 ml., and all these had positive results of Nonne-Apelt and Pandy tests. In 73 of 75 patients with syringomyelia the cell count was normal, and in 70 the protein was below 100 mg/100 ml. In only 4 of 22 patients with subdural hematoma was there an increase in cells; on 2 occasions it was between 5 and 10 per cubic millimeter and in the other 2 cases it was between 11 and 20 per cubic millimeter. A slightly straw-colored fluid was seen only twice. The authors' findings in 238 patients with spinal tumors were similar to those previously reported. The findings in the 770 cases of neurosyphilis were also similar to previous reports. Only 7 of 29 patients with cerebral abscess had faintly turbid cerebrospinal fluid. The only significant feature from this study was that the preoperative fluid may contain neither an increased cell count nor a raised protein content.

ECHOLS, New Orleans.

MYOCLONIC CEREBELLAR DYSSYNERGY OF RAMSAY HUNT. J. CHRISTOPHE and J. GRUNER, Rev. neurol. 95:297, 1956.

The authors report the case of a man who at 27 years of age developed violent myoclonic jerks, limited at first to the right hand, later involving the trunk, and ultimately affecting his gait and speech. There was evidence of cerebellar dysfunction. The EEG showed generalized delta activity. He died about 30 years after the onset of the illness. There was evidence of degeneration of the posterior columns and spinocerebellar tracts of the spinal cord, and atrophy of the olivary and restiform bodies and of the vestibular nuclei. There were marked loss of cells, demyelination, and gliosis in the dentate nucleus, brachium conjunctivum, and red nuclei. The cerebral and cerebellar cortex were relatively unaffected.

BERLIN, New York

THEORY AND FACT IN THE CLASSIFICATION AND INVESTIGATIVE METHODS OF APHASIC DISTURBANCES. E. BAY, Psychiat. et neurol. 134:298 (Nov.) 1957.

Bay stresses the importance of viewing the aphasia problem as a complex, goal-directed attainment, as opposed to impairment of a specific function. The importance of viewing aphasic disturbances against the background of the premorbid speech patterns of the patients so affected is strongly stressed. He emphasizes that many of the classifications of aphasia, especially the Lichtheim-Wernicke, lend themselves poorly to such evaluations, inasmuch as they tend to analyze phenomena in terms of various functions. The simpler classification of receptive *vse* expressive aphasia of Weisenburg and McBride, while somewhat grosser, tends to cover the various exigencies with greater accuracy and enables understanding of many of the otherwise incongruous results.

PARSONS, Montrose, N. Y.

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CEREBELLAR ABNORMALITY AS A POSSIBLE FACTOR IN AMENIA IN A CASE OF MICROCEPHALY.

P. GLEES and F. E. JAMES, Psychiat. et neurol. 134:362 (Dec.) 1957.

Glees and James describe the autopsy findings in a patient with severe microcephalic amentia, who died at the age of 20 years. The outstanding finding was a pronounced loss of Purkinje cells of the cerebellum. The authors speculate on the relationship between this finding and the amentia and are inclined to regard this as an expression of a defect in the cerebellar-activating centers, projecting both to the cerebral cortex and to the bulboreticular formations, which has been described by Magoun and Snider. The similarity of the amentia to the state of apathy resulting in a relative suppression of activities contributing to general intelligence is emphasized by these authors as an indication of the operation of this mechanism. Further relationships between the primary sensory areas for vision and audition and the cerebellum, as demonstrated by Snider, are also acknowledged.

PARSONS, Montrose, N. Y.

HISTOLOGICAL STUDIES IN TEMPORAL LOBE EPILEPSY BASED ON BIOPSY MATERIALS. C. HABERLAND, Psychiat. et neurol. 135:12 (Jan.-Feb.) 1958.

Haberland made histological studies of biopsy material from the brains of 47 patients with temporal lobe epilepsy. The commonest alteration noted was that of sclerosis of the cornu Ammonis, closely followed by cortical and subcortical scars and angiomatic malformations, with less frequently noted lobar sclerosis, diffuse meningeal fibrosis, arachnoidal cyst, and posthemorrhagic subcortical cicatrization. There is much speculation concerning the significance of the anatomical lesion supposedly responsible for epileptiform convulsions; but, inasmuch as a lesion was found in less than 50% of the cases, the anatomical substratum for the physiological disturbances has not as yet been identified, and the dictum that one cannot differentiate a lesion capable of producing convulsions on the basis of its histological characteristics remains unrefuted.

PARSONS, Montrose, N. Y.

CEREBRAL FAT EMBOLI. M. RITZMANN, Psychiat. et neurol. 135:301 (April-May) 1958.

Ritzmann reports 10 patients with cerebral fat emboli, of which 8 had necropsy studies. On the basis of experience with these cases and copious correlation with pertinent literature, a comprehensive picture of cerebral fat embolism is developed. Especially stressed is the differentiation between cerebral fat embolism and acute traumatic subdural and epidural hemorrhage. Valuable aids in the recognition of cerebral fat embolism are the following: the presence of fracture of an extremity as opposed to a skull fracture; a somewhat longer "free interval" between the traumatic episode and the development of cerebral symptoms; the frequent premonitory pulmonary symptoms; tachycardia rather than bradycardia; a higher incidence of fits; funduscopic visualization of fat embolism and distal ischemic retinitis; purpuric skin and conjunctival lesions, and fat in the sputum and urine. Burr holes are always indicated in doubtful cases, and the results will, of course, be negative in cerebral fat embolism. Of especial interest is the author's discussion of prophylaxis of fat embolism by brief fracture-reduction measures, involving a minimum of manipulation and compression, treatment of shock, use of controlled hypotension and hibernation, and, finally, brief mention of application of successful experimental techniques for saponification of intravascular fat.

PARSONS, Montrose, N. Y.

CLINICAL ASPECTS OF CAVERNOUS ANGIOMAS OF THE RHOMBOID FOSSA. F. A. SABURENKO and A. V. LEVITSKAIA, Zhur. nevropat. i psichiat. 57:472, 1957.

A detailed clinicopathological description is given of the rare localization in two cases of the main portion of a cavernous angioma in the upper triangle of the rhomboid fossa, involving also the floor of the fossa. The clinical picture of the two cases cited consisted in the symptoms of a midline tumor, affecting also the nuclear groupings and the conducting system of the floor of the fourth ventricle. After a lengthy remission (one and one-half and two years, respectively), there was a sudden and stormy deterioration in the last stage of the illness, leading rapidly to a fatal issue. Repeated hemorrhages into the tumor were morphologically confirmed by the deposition of hemosiderin and by the impregnation of the connective tissue structures with layers of iron. In one case the angioma was multiple. Where a vascular tumor is suspected, lumbar and ventricular punctures must be performed with the utmost care, as even a slight dislocation may lead to further hemorrhages. The author quotes a case in which death occurred three hours after ventricular puncture.

GOLLAND, Moscow.



SECTION ON
PSYCHIATRY

A Therapeutic Community with an Open Door in a Psychiatric Receiving Service

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A therapeutic community with an open door has been in operation since December, 1956, in the psychiatric receiving service of the county hospital in San Mateo. This paper will point out that such a program can be successful with acutely disturbed patients even when no screening of admissions is permitted.

History

Acting on the modern theory that the mentally ill are best treated as near home as possible, the Board of Supervisors and the Department of Health and Welfare of San Mateo County, with the help of a bond issue, established a 30-bed psychiatric ward as part of the Community Hospital of San Mateo County. The purpose of the ward is to provide for observation and diagnosis of indigent psychiatric patients and to avoid commitment to state hospitals by treating and rehabilitating as many as possible locally. Hospitalization is thought of not as an isolated experience but as one phase of a treatment program which must begin and end in the home community.

Previous to the establishment of the ward, mentally ill patients and alcoholics were cared for in locked single rooms scattered throughout the building. Hospital staff, local police forces, and the community in general were unfamiliar with the idea of

a therapeutic community and had long been used to locking up patients, believing this to be necessary for the safety of everyone. Considerable doubt and apprehension were evident when an unlocked ward was proposed. There was great anxiety about suicides, escapes, and violence which might lead to destruction in other parts of the hospital or in the community, and about legal suits for damages. To date, these fears have not proved justified. Serious problems have arisen, but none which indicate that a therapeutic community and an open door are not possible and helpful.

Statistics

The ward opened on Nov. 30, 1956, with seven patients. By March, 1958, a total of 1,624 patients had been admitted, for an average stay of 7.19 days. Monthly admissions have averaged 101.5. The average daily census has been 25.6. The total patient-days during the past six months have averaged 747 per month. About 37% of the patients admitted have been diagnosed as alcoholic. The other diagnoses have been psychoses, 26%; neuroses, 10%; character disorders, 13%; senile dementia, 8%; other organic conditions, 5%. With the exception of a limited number of voluntary admissions, the patients are hospitalized for observation by order of a judge or by a peace officer. Such patients cannot be refused admission, and no screening is possible. All patients, regardless of diagnosis,

Submitted for publication July 27, 1958.
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sex, or severity of illness, are treated on the same ward. The physical facilities are new and attractive but somewhat too small, considering the number of patients requiring care.

The staff at first was small, but now consists of 2 full-time psychiatrists, 1 full-time occupational therapist, 1 full-time and 1 part-time psychiatric social worker, 1 full-time and 1 part-time secretary, and 15 nursing personnel (8 registered nurses, 5 vocational nurses, and 2 attendants) to cover the three shifts. Only two of the nursing personnel are men. With the exception of the psychiatrists, the social workers, and one nurse, the personnel had had little previous psychiatric experience. The nursing personnel were recruited from the other services of the general hospital.

Basic Philosophy

In this setting an attempt has been made to establish a psychiatric service based on the principle of unrestricted communication between patient and staff and on the principle of maximum utilization of the healthy part of a patient's personality. The first principle, that of adequate communication and mutual understanding, implies, of course, courtesy and consideration for everyone, patients and staff alike. It requires a willingness to meet with, talk to, and think about patients as deserving human beings with equal human rights. It demands an end to the frequently observed alarm reaction of old-line employees in traditional hospitals, who fear that they may be taken in by the patient and made to look foolish. Such employees often assume that the patient will "talk crazy." As a result, the employees may be inattentive, unhearing, or, in some cases, actually rude. Under such circumstances, any useful cooperation or communication is impossible.

Mutual understanding requires a minimum of authoritarianism and a willingness to understand and to plan together. Any barriers to communication, such as open or covert hostility, excessive drives for status and prestige, and overwork, must be recog-

nized and modified as quickly as possible. Any community which is truly therapeutic, or, indeed, tolerable, must have an adequate communication system.

The second principle, that of utilization of the healthy parts of a personality, is also extremely important. Traditionally, physicians have been concerned with pathology. The development of strength and assets has, at times, been overlooked or left to the social workers, occupational therapists, or others. Therapeutic communities, while not overlooking or ignoring the illness itself, have begun to place emphasis on the healthy aspects of personalities. No patient, unless he is extremely toxic or otherwise seriously impaired organically, is totally without some assets which can be mobilized for group living. Refusing a patient the opportunity to use his strengths may cause him to lose them.

Patients are encouraged and expected to behave properly and to become part of the group. This expectation is very therapeutic. It rightfully places the major share of the responsibility for improvement upon the patient himself and makes unnecessary most of the old restrictive precautions against suicide, violence, and aggressive behavior. Patients generally accept the expectations of the group around them.

There are only three items excluded from the ward: liquor, razor blades, and personal medication. Items such as scissors, mirrors, and nail files are considered useful and necessary. Suicidal attempts and aberrant behavior are not expected or condoned, and seldom occur. Furthermore, when trouble develops, it is usually because a patient or a small group is excluded from or has refused to accept the "expectation of success" and has not become a part of the total therapeutic community. Occasionally, for example, we have a small group of "acting-out" juveniles. Our first such group seriously disturbed the ward before it was realized that the adult group had expected childish aggression and had received what had been expected. The teen-agers had stopped coming to the daily group meetings,

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slept during the day instead of at night, etc., which further isolated them from the group. The problem was solved only by insisting on attendance at the general group meeting and by examining the adult feelings and attitudes about the younger group.

Another example of the effect of the "expectation" has been the rather dramatic change in some patients when they first come onto the ward. Violent and struggling patients, usually inebriates or paranoid schizophrenics, are occasionally brought to the ward in shackles by local police officers. When this happens, shackles are removed as quickly as possible, and the police are asked to leave the ward. The patient is confronted by an ununiformed nurse, often alone, who occupies herself in making him comfortable. She answers his questions courteously and in a friendly manner. She does not demand that he take off all his clothes, give up his personal possessions, or submit to a rectal temperature unless these measures are really necessary. She treats him with respect and expects to have this returned. So far, none of our nurses have been injured. Angry aggression appears to be closely related to a specific stimulus in the immediate environment.

The Role of the Group

In our particular therapeutic community, the ward group, composed of both patients and staff, is the chief therapeutic instrument. This group has assumed the direction of, and the responsibility for, a great part of the daily life. Being part of a larger community, the ward must abide by general rules wherever they apply; within these limits the group makes its own rules. The total group meets daily at 9:00 a. m., and everyone who is physically able is expected to attend. Each member has one vote, the majority ruling. The ward psychiatrist has veto power and uses it only as absolutely required. The patient's progress is evaluated in terms of his group relationship; that is, the patient is generally "doing well" and getting well when he is comfortable with and responsible toward the group. Like-

wise, the group is therapeutic to the extent that it can understand and adapt itself to the needs of the individual. The staff, also, may be partially evaluated in terms of its group relationships, both within its own staff group and within the larger ward group.

Some examples of functions which the patient group assumes are the watching of the open door to see that confused or frightened patients do not wander out, the serving of meals to ambulatory and bed patients, general housekeeping, welcoming of the new patients, issuing of pass cards which carry the privilege of visiting off ward and planning on-ward and off-ward activities.

As part of the therapeutic community program, a number of special activities, such as arts and crafts, gardening, housekeeping, and the use of the kitchen, have been encouraged. The kitchen has been the focal point of much activity, many problems, great emotion, and considerable therapy. Everyone has access to it at all times, night and day. Keeping it orderly—keeping the coffee cups from piling too high in the sink—has been a daily problem. Much necessary and helpful thinking about the setting of reasonable limits has been stimulated by this problem. In retrospect, the kitchen has provided the most useful therapeutic experience of the ward.

The Intensive Treatment Group

After admission to the ward, patients are examined and evaluated as rapidly as possible to determine what form of treatment is most suitable. A majority of the patients are returned to home and community within a week. A minority is transferred to other hospitals and nursing homes. About eight patients at any one time are selected for an intensive-treatment group. These patients may stay three months and are selected on the basis of diagnosis, prognosis, family conditions, receptivity to psychotherapy, and the ability to join the group or to lead it. They form the nucleus of the larger community group, a stable core

group, which is necessary in view of the large number of admissions and the short length of stay. These patients hold offices, serve as welcomers, and, in general, bear the culture from one transient group to the next.

Other Therapies

In addition to the therapeutic community, other standard forms of psychiatric therapy are available on the ward. The tranquilizing drugs are used liberally, but decreasingly as the community has become more truly therapeutic. Formal psychotherapy is increasing as more therapists become available. Electric shock treatment is rarely used. Physical restraints have been used only twice, for short periods of time for toxic psychoses in senile persons when drugs are unsafe.

Locks

Locks and seclusion rooms are used rarely, and for short periods in extreme situations. They are never thought of as treatments in themselves but are considered failures in treatment. They are the last things to be thought of, rather than the first, since enforced isolation almost always leads to regression and exacerbation of symptoms. When the ward first opened, the matter of locks was a major concern of nearly everyone and quickly became a symbol of the entire program. Those who disapproved of anything frequently focused on the lack of locks and safeguards; those who supported the program came to feel that the use of locks would destroy everything. As the ward has become better established and regulated, however, the problem has come into better focus. Locks, though occasionally necessary, are used only in real emergencies, when all else fails. Locking a patient up may handle the staff's problem but seldom the patient's.

Evaluation

The formal evaluation of the success or failure of the ward as a therapeutic community has not been adequate because of

the short time involved and the absence of personnel for follow-up study. There have been a large number of favorable comments from patients, relatives, and observers. People who formerly were severe critics are now staunch supporters. Objectively, the statistics appear favorable. Of the number of patients admitted, 68% have been returned to the community after an average stay of seven days. There have been no suicides, although there have been two attempts, one of which was provoked by an unsympathetic staff member. There has been no violence resulting in serious injury. There have been many unauthorized absences from the ward, but most patients return voluntarily or with a minimum of urging. There were three instances of minor property damage off the ward and one instance of minor personal injury, but no damage suits. About 28% of admissions have been referred voluntarily or by commitment to state or other hospitals. The majority of these patients have been chronic organic psychotics, chronic functional psychotics, and chronic alcoholics, but some have been acute psychotics, for whom there was not room for a prolonged stay on our 30-bed ward. Of the 1,624 patients, however, there have been only 4 who probably could not have been treated on our ward with an open door. Two of these were acutely paranoid young women who had the unusual ability to appear completely relaxed and cooperative coincident with feeling extremely paranoid. Both faithfully promised not to leave the ward without permission, and then did so at the first opportunity. After several such episodes for each patient, we came to the conclusion that the risk of keeping them on an open ward was too great to take, although neither patient caused any serious trouble while away from the hospital. The other two were large, angry manic male patients, who refused to take oral medicine or to allow intramuscular injections.

In general, we have found that the manic patients are the most difficult to treat in this setting, depressive patients being the next

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most difficult. Schizophrenics, alcoholics, and patients with character disorders have responded well.

Problems

It has been stated occasionally that the success of the open-door policy probably depends upon the availability of a locked state hospital nearby which can be used for buck-passing purposes. While it is certainly true that there have been some patients who could not be treated in this setting, it is also true that more than 99% of admissions have been cared for satisfactorily. This is despite the fact that the treatment area is not designed or equipped for the long-term care of chronic patients; that it is not adequately staffed with male attendants to handle large, desperate paranoid men, with or without the help of locks; that the presence of both men and women patients on the ward, while helpful to most people, is difficult for some, and that the second-floor location and the lack of outside recreation areas cause some patients to feel confined. Having only one ward which must care for the sensitive schizophrenics, belligerent manics and alcoholics, demented senile patients, acting-out juveniles, and guilty depressives—all at the same time—makes for problems. But, far from detracting from the value of a therapeutic community and an open door, the above problems make even clearer the value and the necessity of rapid mobilization of an effective patient group with open lines of communication.

There have been other important problems which we have had to face. Initially, the major problem was convincing people that the idea of a therapeutic community and an open door was sound. This was done partly through formal and informal meetings and discussions, and partly through gradual attrition of opposition by not having major trouble. This could not have been done without the consistent (and often minority) support of the top medical administrator of the Health and Welfare Department of this county. The problems of interpretation of

the program continue, but the struggle for existence which characterized the early months has subsided considerably.

In its place has emerged the problem of being too busy. Admissions are unscheduled and rapid, and finding bed space is often difficult. These factors put considerable strain on the principle of personal consideration which underlies any psychotherapeutic technique. At the same time, they make all the more necessary a patient's organization which can assume some of the nursing functions.

Isolation

A further word about communication is important. In addition to the necessary lines of communication within the ward group, it is advisable to keep close contact with other parts of the hospital, with community agencies, volunteer groups, and police forces, as well as with the patient's families. A constant effort is made to keep the degree of isolation at a minimum. There is a public telephone on the ward, available to the patients; visiting hours are twice daily, and relatives may visit from the first day, unless this is obviously upsetting to the patient. The safety of the hospital, of the family, and of the community is protected as much as possible—not necessarily their complacency. The mentally ill still deserve to be heard. Sometimes the community has to listen, whether it prefers to or not.

Conclusions

It is too early to have reached any final conclusions about such a program in a county receiving hospital. However, several preliminary impressions may be noted.

1. It is possible to develop a therapeutic community with an open door in a county hospital, based on the twin principles of adequate communication and maximum utilization of the healthy personality factors.

2. The open door is not possible without the therapeutic community, because, in the absence of a huge staff, the patients must organize and accept responsibility for it.

3. Schisms in the group or ostracisms from it are disastrous and must be dealt with promptly. It is imperative for new patients to join the group quickly. This can be accomplished by welcoming committees and by any therapy which will make the patient feel accepted and wanted. The staff must cooperate in this effort but must not undermine the group's authority or function.

4. Arbitrary or unnecessary controls from outside the group make a democratic therapeutic community very difficult, if not impossible, and controls from within are far more effective. However, when these controls are absent or poorly developed in individuals, control of that individual by the group is necessary and desirable. In rare instances the staff must provide external controls temporarily for the group. Unrestricted permissiveness in the absence of controls from within leads to anarchy. Authoritarianism, when applied to the mentally ill, leads to further regression and withdrawal.

5. When a new philosophy is being tried, there is an advantage in recruiting a nursing staff from among people without previous psychiatric training unless that training has been consistent with the new philosophy. Finding basically mature and comfortable people is the major consideration.

6. A program of this type is easier only for the patient. The staff works harder and feels more anxiety. When locks are not relied upon, the ability to communicate is often put to a severe test. Satisfactions in this type of program are great, however, and only one staff member has left because of dissatisfaction.

7. A therapeutic community can be as safe for the community at large as a custodial program. An unlocked door implies the acceptance of some risk, but the therapeutic milieu which results seems to reduce the incidence of major difficulty. Nothing has happened so far to indicate an undue risk in this program.

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A Mental Syndrome Associated with Lung Carcinoma

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The neurological disorders which may occur in association with carcinoma, in the absence of demonstrable metastatic deposits in nervous tissues, have aroused increasing interest in recent years. The combination of sensory neuropathy and bronchial carcinoma described by Denny-Brown,¹ and concurrently by Wyburn-Mason,² has been the subject of reports by many later writers, including Henson, Russell, and Wilkinson³; Heathfield and Williams⁴ and Smith and Whitfield.⁵ Brain, Daniel, and Greenfield⁶ describe four cases of subacute cerebellar degeneration, three of which were found in association with carcinoma of the lung or ovary, and refer to two earlier cases described by Greenfield in 1934. That a wide range of unusual neurological disorders accompanies carcinoma with significant frequency is stressed by Henson and associates³ in their large series of 19 cases, which comprises 5 cases of cerebellar disease, 3 of sensory neuropathy, 3 of polyneuritis, and 8 of neuromuscular disorders (muscular neuropathy and myopathy). This series also illustrates the predominance of the bronchus as the site of the accompanying tumor, since 17 of the 19 patients had a bronchial carcinoma. The two exceptions were cases of cerebellar disease occurring with (a) ovarian carcinoma and (b) carcinoma of the breast. The diversity of the neurological concomitants of carcinoma is reemphasized by Smith and Whitfield,⁵ who point out that, in addition to such relatively discrete entities as sensory neuropathy and subacute cortical cerebellar degeneration, "myopathy, mixed types of polyneuritis involving both peripheral and cranial nerves, pyramidal tract

lesions and *mental changes* [italics ours] occur sometimes in pure forms but more often in varying combinations."

It is true that mental symptoms are mentioned in some of the aforementioned cases, but usually as an incidental finding and most frequently in cases of cerebellar disease. Of the four cases described by Brain et al.,⁶ Patient 1 showed at the outset loss of interest in housework and unpleasant, confused dreams, and subsequently progressive mental deterioration, Patient 2 showed progressive dementia, and Patient 3 was described as wandering in the mind with lucid intervals—she was rational one moment and talked nonsense the next. Of the five patients with cerebellar disease in the series of Henson et al.,³ Patients 1 and 3 were euphoric and mildly demented; Patient 2 was anxious and forgetful, while Patient 5, although fully oriented, showed anxiety so gross as to necessitate leukotomy. Of their cases of neuropathy, Patients 6 and 8 were said to show a marked hysterical overlay, and Patient 9 showed memory defects. Patient 19 (predominantly myopathic) was at first anxious but later became euphoric.

So far as we are aware, mental symptoms "in pure form" accompanying carcinoma uncomplicated by cerebral metastases have been described only by Charatan and Brierley.⁸ The mental syndrome displayed by their three patients, all of whom had a bronchial carcinoma, "resembled a fluctuating toxic confusional psychosis in which 'lucid intervals' were well marked," and there were no associated neurological signs. Charatan and Brierley⁸ assume this mental syndrome to bear the same relationship to the underlying carcinoma as do the neuropathies described by other writers. They refer specifically to the etiological theory of

Submitted for publication June 6, 1958.

From the Royal Edinburgh Hospital for Mental and Nervous Disorders, Craig House Section.

sensory neuropathy propounded by Denny-Brown,¹ i. e., that a by-product produced by the carcinoma interferes with the biological conjugation of pantothenic acid in metabolism. At the same time, their discovery at autopsy of extensive liver metastases in each of their cases leads them to speculate on the role of "liver damage" as a possible accessory factor in the production of the mental symptoms. In view of this latter doubt, it seems worth while to report two cases similar to those described by Charatan and Brierly² in which liver metastasis was either minimal or absent.

Report of Cases

CASE 1.—A housewife aged 50 was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders on Sept. 11, 1950. There was no family or personal history of mental illness. The patient had always been healthy and was a nonsmoker, with predominantly athletic interests. She was happily married, with one son, aged 11 years. The details of the present illness were obtained from her husband, who, unfortunately, was a poor witness; moreover, his recent employment had imposed frequent absences from home. In July, 1950, she became restless, apprehensive, and "difficult." She worried about money, believing she had none. She was confused about dates and time, but was correctly oriented as to place. A two weeks' holiday appeared to effect an improvement, but she relapsed a week after her return home. She then believed that the police were coming for her, that people were prowling around her house at night. She expressed fears of developing tuberculosis and mental illness. On one occasion, she said that she would kill herself, if only she had a big knife.

On admission, she appeared distraught. Answers to questions were slow and delayed. She kept her face averted, saying that she was unable to face her interrogator because of the dreadful things she had done. Every sound in the ward seemed imbued with fatal significance for her; e. g., she started on hearing a bell, saying: "That's a bell. Why don't you finish me off now?" She enumerated the colors of common objects around her, seeming to read a special significance in their coloring. Assessment of her intellectual faculties was difficult because her attention could not be held. She gave the correct month but not the day, and said that her present domicile was Edinburgh Castle. She could not give the dates of her birth or marriage, or of the Second World War, and could not repeat, after a lapse of five minutes, several

items recited to her. She could not essay calculations. She gave the capital of the United States as New York and that of France as Paris, and, on being asked to name some rivers in Scotland, she replied that there were millions.

Her healthy, sunburned appearance and lean, muscular physique suggested an active outdoor life. No physical abnormalities were elicited apart from a blood pressure of 190/110 and a minor degree of parrot-beak clubbing of the fingers.

This condition of extreme fear and agitation seen on admission progressed over the following three weeks to a state indistinguishable from that of depressive stupor with refusal of food. Because of this last, she was given two electrical convulsions in conjunction with thiopental (Pentothal) and relaxant drugs, a week elapsing between treatments. No apparent benefit ensued. Thereafter she developed a pain in the chest with signs of pleural effusion at the left base. Radiological examinations on Oct. 5 and Oct. 10 corroborated the presence of a pleural effusion with underlying consolidation, the radiographic appearances being suggestive of neoplasm. Fluid aspirated on Oct. 12 contained carcinoma cells.

In the two weeks preceding her death, on Oct. 21, the patient showed episodic improvement in her mental state in that periods of relative lucidity alternated with periods of stupor.

*Autopsy Finding:**—A tumor arising from the stem bronchus to the left lung formed mass in the hilus 4 cm. in diameter. There was extensive lymphatic spread in the left lower lobe, and the left hilar lymph nodes were enlarged and infiltrated by tumor. Subpleural lymphatic spread had also occurred in the left upper lobe with extension into the parietal pleura at the apex. An embolus was present in the pulmonary artery to the left upper lobe, and the left femoral vein was thrombosed. Two small subcapsular metastases, measuring only 2-3 mm. in diameter, were found in the liver. The right adrenal gland contained a single metastatic lesion, 1 cm. in diameter, and the left adrenal gland, two small tumor nodules, measuring 2-3 mm. in diameter. There was no naked-eye evidence of tumor deposits in brain substance or meninges. The histological picture in both primary and secondary tumors was that of an anaplastic carcinoma, the neoplastic cells showing considerable pleomorphism and mitotic activity. Histological examination of brain sections revealed neither metastases nor any other significant abnormality.

At the time this first case was seen—two years after Denny-Brown's¹ report—it was

* The autopsy was performed by Dr. A. Macfarlane, of the Department of Neuropathology, University of Edinburgh.

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thought that this syndrome, with its mixture of psychotic depression and intellectual defects, might represent a "mental" analogue of the somatic neurological manifestations described by Denny-Brown¹ in association with bronchial carcinoma. It seemed unjustifiable, however, to draw conclusions from a single patient, who, moreover, lapsed into a state of inaccessibility which continued (with only brief lucid intervals in the terminal phase) until her death, within six weeks of admission. The second patient was seen at an earlier stage, survived for six months, and could therefore be studied in more detail.

CASE 2.—A widow, aged 56, employed as a stenographer, was first seen as an outpatient on May 29, 1956, with the complaint that for the last six months she had felt generally unwell and unlike her former self. She described an overhanging sense of fear, inability to concentrate, sensations of pressure and numbness over the vertex, and a heavy feeling in the epigastric region. She had the impression that her work was deteriorating and, as an instance of this, cited her frequent inability to understand the gist of telephone communications. Twice she experienced attacks of generalized "trembling," accompanied by acute terror. The second of these led to her investigation in a medical outpatient department, where no physical abnormality was elicited. A teetotaler and nonsmoker, her only previous illness of note had been an attack of acute influenza in 1934, associated with a high temperature but no mental disturbance. Her husband, who had died of coronary thrombosis five years previously, had been a marine engineer, and the nomadic life which his profession imposed on his family allowed of a useful indirect assessment of the patient's memory functions. She readily enumerated the family's frequent changes of abode and their appropriate dates. The tentative diagnosis made was that of depression, and she was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders (Craig House Section) on June 6, 1956.

After admission, a more florid depressive thought content was evident. She insisted that she had brought all this on herself, and that nobody could help her. She was tearful, required encouragement to eat, and slept fitfully, even with sedation. She then showed intellectual impairment, making many mistakes and omissions when supplying her previous history. Two days after admission she had a brief episode of faintness associated with tachycardia. Detailed physical examination revealed no abnormality, apart from a persistent wheeze in the

left axilla. During June 21-22 she appeared episodically delirious, with bursts of shouting and retching, but thereafter reverted to her former state of quiet depression. On June 27 she gradually relapsed into a more sustained delirious state, mumbling stereotyped phrases, misidentifying her attendants, and making smacking movements with her lips. Coincidentally, her temperature rose to 100 F; auscultation revealed complete absence of breath sounds over the left chest, and she became rapidly dehydrated. Although no focal neurological signs were present, the possibility of cerebral metastases or a primary cerebral tumor was considered. Cerebrospinal fluid findings were normal. The EEG showed theta activity posteriorly in both hemispheres but no other abnormality. An x-ray of the chest was reported as showing thickening of the pleura and inflammatory changes in the left lung. In the course of a few days, the acute delirium subsided into a state of profound apathy, with dulling of comprehension. Examination on July 2 revealed a gross tremor of the outstretched hands. Although there was no clinical evidence of liver disease, this combination of tremor and mental symptoms appeared to warrant consideration of the hepatic coma syndrome (Adams and Foley).² Liver function tests were carried out, and the patient was put on the prescribed hepatic coma regimen (Sherlock³), including intestinal disinfection and withdrawal of all dietary proteins. An accelerated improvement in her mental state ensued. Yet, apart from raised blood ammonia levels, all liver function tests gave normal findings (see below). Moreover, the patient's return to normal mental alertness was maintained and consolidated on the exhibition of a high-protein diet, with the provocative addition of ammonium salts and methionine. Meanwhile, the abnormal pulmonary signs persisted, and on Aug. 9 a bronchoscopic examination proved the existence of an undifferentiated round-cell carcinoma of the bronchus.

Total protein	6.38 gm. %
Albumin	4.37 gm. %
Globulin	2.01 gm. %
Zinc turbidity	2.6 units
Thymol turbidity	0.2 units
Bilirubin	0.3 mg. %
Alkaline phosphatase ..	6 units (King-Armstrong)
Cholesterol	130 mg. %
Cephalin-cholesterol flocculation test	Negative
Fasting blood sugar	106 mg. %
Sulfobromophthalein (Bromsulphalein) excretion	Within normal limits
Blood ammonia nitrogen (Conway's method), $\mu\text{g.} \%$	
July 3	320
July 5	210

The patient remained intellectually alert and emotionally composed (the depressive symptoms

present on admission did not reappear) until the latter half of August, when episodes of agitation and disorientation, lasting one to two days, recurred on three separate occasions and were followed in mid-September by a more prolonged period of mental confusion. This last was accompanied by profuse sweating, and investigation of the blood chemistry at this time gave the following findings:

CO ₂ -combining power	60 vol. %
Blood urea nitrogen	11 μ g. %
Serum sodium	298 μ g. %
Potassium	16.8 μ g. %
Chloride	480 μ g. %

(The low serum sodium and chloride were attributed to the sweating and unrestricted drinking of water.) There then set in a more accelerated decline in both the physical and the mental sphere. Lucid intervals become shorter and more infrequent. During the last two months of her life, the patient was continuously drowsy and confused; yet the characteristic fluctuation in her mental state continued, in that bouts of acute delirium, lasting up to five days, were superimposed on the general picture. She died on Dec. 3, 1956.

Autopsy Findings.†—A very large tumor was arising in relation to the left main bronchus, which, together with its branches, was considerably narrowed by direct involvement of its walls. The intrapulmonary neoplasm was irregular in shape and on section measured 9 cm. in its maximum diameter. It was composed of soft necrotic tissue, and its exact site of origin was no longer detectable. This mass was continuous with a large hilar and mediastinal mass of neoplastic lymph nodes, which encircled the right and left pulmonary arteries and was adherent to the arch of the aorta. No metastases were demonstrated. Histological examination showed that the tumor was an anaplastic small round-cell carcinoma.

The weight of the brain after fixation was 1,600 gm. The leptomeninges were healthy. There was slight, opaque thickening of the arteries of the circle of Willis, but no severe degree of atherosomatous change was found. Serial coronal section showed no abnormalities of the cerebrum, and the brain stem and cerebellum were likewise normal externally and on section. Histological examination of sections of cortex and basal ganglia revealed no particular abnormalities in either gray or white matter. Occasionally one or two foam cells containing hemosiderin pigment were seen in the perivascular spaces. The ependymal lining of the ventricular wall appeared normal. Within the cerebellum, there was in some places a probable proliferation of Bergmann's layer, but this was not

associated with any decrease in the numbers of Purkinje cells. The molecular and granular layers were normal, as were also the white matter and dentate nucleus.

Comment

The mental symptoms in Case 1 appeared 2 months before the physical signs of pleural effusion and 3 months before death; those in Case 2 arose 6 months before clinical evidence of pulmonary disease and some 12 months before death. In two of the cases reported by Charatan and Brierley⁸ mental symptoms preceded the signs of pulmonary neoplasm by four and six months, respectively. A similar observation has been made for the carcinomatous neuropathies, Henson et al.³ reporting that "neurological symptoms preceded those directly due to the carcinoma or diagnosis of the growth in 15 of 19 patients."

There was no clinical evidence of neuropathy, myopathy, or cerebellar disorder in our two patients, and this was similarly lacking in Charatan and Brierley's⁸ series.

Mental symptoms characteristic of psychotic depression gave rise to initial difficulties in diagnosis. The first patient on admission was retarded in speech and action and expressed florid delusions of guilt. But her concomitant intellectual defects seemed to be too severe to be attributable wholly to depressive preoccupation and argued an organic basis. Patient 2, at initial outpatient interview, described the overhanging sense of fear and the bizarre paresthesias related to the head and epigastrium, so frequently described in involutional depression. Following admission, her mood became more overtly depressed. Yet her confession that she had had difficulty, while at work, in understanding the gist of telephone conversations suggested previous mild (and possibly episodic) intellectual impairment, and this last became more prominent after admission to hospital, when she made mistakes and omissions in retailing her history. In both Cases 1 and 2 these initial and variable affective and intellectual disturbances progressed to a state of phasic alteration in consciousness. When viewed in retrospect,

† The autopsy was performed by Dr. A. F. J. Maloney, of the Department of Neuropathology, University of Edinburgh.

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this clinical picture closely resembled the "fluctuating confusional state with lucid periods" described by Charatan and Brierley.⁸ This aggregation of symptoms was, in fact, indicative of a subacute organic reaction, and not of a "functional" psychotic state.

In neither of our two cases was any significant abnormality found on macroscopic or microscopic examination of the brain. A similar difficulty has been experienced in correlating the sporadic mental symptoms seen in the carcinomatous neuropathies with a structural cerebral lesion (Brain et al.,⁶ Henson et al.³), although well-defined pathological changes, often severe and including neuronal loss, have been demonstrated for the somatic manifestations, (Denny-Brown,¹ Brain et al.,⁶ Henson et al.,³ etc.). In the wholly mental syndrome associated with bronchial carcinoma described by Charatan and Brierley,⁸ minimal cerebral abnormalities were demonstrated at autopsy. These authors conclude from their particularly exhaustive histopathological examinations that the only finding of possible significance was "a marginal, subependymal and white matter gliosis." Such reports of absent or minimal cerebral abnormality suggest that the mental symptoms found in association with carcinoma may be based on a biochemical, and not on a structural, lesion. Minor and nonspecific EEG anomalies were recorded in our Case 2 and in one of Charatan and Brierley's⁸ cases. This recalls an isolated observation of Gastaut, Roger, and Chatrian,¹¹ who demonstrated similar minor EEG abnormalities in 10 of a series of 22 cases of bronchial carcinoma without cerebral metastases. Unfortunately, no reference is made to the mental status in these 10 cases. The authors state that they are unable to explain these abnormal EEG findings, but discuss *inter alia* a possible metabolic disturbance.

Reference has already been made in our introduction to Charatan and Brierley's⁸ attempts to elucidate the etiology of the mental syndrome in their three cases of bronchial carcinoma. Since each of their cases was

found at autopsy to have extensive liver metastases, they found it difficult to state how much liver damage per se contributed to the genesis of the psychiatric picture. Our two cases would appear to eliminate "liver damage" as a contributory factor. In Case 2 a battery of liver function tests performed during a period of mental confusion gave normal results except for a raised blood ammonia nitrogen. After the return of mental clarity, a high-protein diet, reinforced with ammonium salts and methionine, to which patients with liver disease are known to be sensitive (Phillips, Schwartz, Gabuzda, and Davidson;¹² Sherlock, Summerskill, White, and Phear¹³), caused no recrudescence of symptoms. Apart from two small subcapsular liver metastases in Case 1, no anomaly of the liver or portal circulation was demonstrated in either case at autopsy.

The significance of the raised blood ammonia nitrogen levels in Case 2 is difficult to evaluate. Since this test is fraught with technical difficulties, we do not wish to stress this finding unduly. On the other hand, we have recently demonstrated a high blood ammonia nitrogen in a third case of lung carcinoma with mental symptoms, and therefore consider that it cannot be ignored. Paradoxically, the study of the relationship between high blood ammonia levels and mental symptoms has been most extensively investigated in the hepatic coma syndrome (Adams and Foley⁹), which we consider can be eliminated in our two cases. Yet opinion on the role of ammonia in the production of the mental symptoms in hepatic coma is not unanimous. Phear, Sherlock, and Summerskill¹⁴ hesitate to ascribe the mental symptoms solely and directly to the raised blood ammonia level because of a lack of complete correlation between this level and the symptoms of coma and pre coma. Conversely, Bessman and Bessman,¹⁵ basing their conclusions on the ammonia content of both arterial and venous blood, consider that "the blood level of ammonia is roughly proportional to the depth of the coma." Walshe,¹⁶ in a critical review, states that, although the role of ammonia in the genesis

of hepatic coma is not yet satisfactorily defined, "there is no other theory that comes so near to conforming to the observed facts."

Liver disease excepted, the other clinical conditions which may be associated with a high blood ammonia are not clearly defined, but Bessman¹⁷ has recently expressed the opinion that "there are a number of clinical situations in which ammonia probably plays a significant role in the pathogenesis of the cerebral symptoms where there is no discernible liver disease." As far back as 1933, Fuld¹⁸ found a raised blood ammonia in association with a wide variety of systemic diseases, including lung infections, and often this rise in blood ammonia occurred when no symptom of liver disease was detectable. In our Case 2, high blood ammonia levels were recorded on two occasions during a phase of subsiding delirium but persisting mental disturbance. These tests formed part of a battery performed at a time when hepatic coma was considered a possible diagnosis. No further estimations were made after hepatic coma was excluded, and the opportunity of correlating blood ammonia levels with the patient's subsequent phases of lucidity and delirium was lost. Further observations on blood ammonia seem indicated in cases of bronchial carcinoma associated with mental symptoms.

The precise relationship which exists between carcinoma and the neuropathies is still unknown. Denny-Brown,¹ impressed by the similarity of the histological changes in his two cases of sensory neuropathy to those seen in deficiency of pantothenic acid and vitamin E in animals, suggested that a by-product of the carcinoma might interfere with the biological conjugation of pantothenic acid in metabolism, and this theory has not so far been superseded. The finding that a wholly mental syndrome can also occur in association with carcinoma still further widens the scope of investigations into the relationship between carcinoma and its neurological concomitants.

Summary

A description is given of two cases in which mental symptoms occurred in associa-

tion with bronchial carcinoma, uncomplicated by cerebral metastases. In both cases mental symptoms preceded the diagnosis of the growth. The psychiatric syndrome consisted of depressive symptoms, intellectual impairment, and alterations in consciousness, all of these components tending to be variable in degree and fluctuating in their course. This variability and fluctuation suggested an underlying biochemical disorder. No structural lesion of the brain was demonstrated at autopsy. The only positive laboratory finding was a raised blood ammonia level in Case 2.

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Studies of Sleep Deprivation—Relationship to Schizophrenia

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Introduction

There were several reasons for investigating the effects of sleep deprivation in man. One was simply a curiosity about the unusual consequences of prolonged insomnia described by earlier investigators. Kleitman¹ and Tyler² cited in detail the hallucinations and "psychotic-like" symptoms that occur under these circumstances and also described subjects who developed short-lived "schizophrenic" psychoses. Psychological alterations, such as inattention, apathy, illusions, and hallucinations, which commonly appear after 36 to 50 hours of wakefulness, have been noted to coincide with an increase in high-frequency, low-amplitude waves on the electroencephalogram.³⁻⁵ In contrast to such spontaneous psychological disturbances, sleep-deprived subjects have been able to perform normally on specific tests designed to measure work capacity, psychomotor performance, intellectual acumen, and personality structure.^{1,8} Measurements of the basal metabolic rate, blood sugar, alkaline reserve, blood and urinary adrenal steroids, etc., have not been found to change significantly with sleep deprivation.^{1,5}

Submitted for publication July 2, 1958.

This investigation was supported in part by funds from the Scottish Rites Foundation.

Roger Allison, M.A., assisted in the selection and application of the psychological tests used in this study.

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An abbreviated version of this paper was presented at the meeting of the Western Division of the American Psychiatric Association on Nov. 21, 1957.

A more pertinent reason for our interest was the hypothesis that sleep deprivation had greater clinical significance in the precipitation of a few schizophrenic reactions than had previously been suspected. It is common knowledge that fatigued children and adults tend to be irritable and unreasonable. It is less commonly emphasized that many agitated persons on the brink of a psychotic break suffer from severe insomnia and that a few pass through a prolonged period of wakefulness as the schizophrenic process unfolds. Two such patients have been studied and will be reported. They have prompted us to inquire whether a prolonged loss of sleep might have a deleterious effect upon the personality of an individual already on the verge of a psychosis. It was hoped that these studies might clarify the importance of this possibility.

Experimental Design, Subjects, and Methods of Observation

In designing the studies, major emphasis was placed upon the measurement of the psychological effects of sleep deprivation. The tests employed were not entirely satisfactory, despite their numbers, since precise psychological tools to appraise the highest and most refined cortical functions are not available. As a reflection of our interest in psychoendocrinology, studies were made also of the concentrations and the diurnal pattern of the blood and urinary adrenal steroids. In a second series of experiments, the effect of *d*-lysergic acid diethylamide (LSD-25) on sleep-deprived subjects was studied to determine the influence of prolonged wakefulness on sensitivity to this

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hallucinogenic agent. Finally, one subject was studied on a metabolic ward to determine the effect of sleep deprivation on protein and electrolyte metabolism.

Seven medical students, motivated by a progressive pay scale, remained without sleep for 72 consecutive hours. During this time, they stayed in rooms on an open psychiatric ward, took their meals in the hospital cafeteria, and were free to stimulate wakefulness by whatever diversions they might choose. To ensure wakefulness, the subjects were constantly attended by relays of monitors, who were also responsible for carrying out behavioral observations and administering the various psychological tests.

In terms of interpersonal relationships between subjects and investigators, the experimental setting was permissive and anxiety-sparing. No efforts were made to irritate, challenge, or otherwise deliberately stress the subjects. The various observations and tests carried out and their timing during the 72-hour experimental period are summarized in Table 1.

The effects of LSD-25 were studied in four subjects who remained awake for 48 hours before receiving the drug. The one subject who was carefully studied metabolically was placed on a constant diet, and, after seven days, when he was in nitrogen, sodium, potassium, phosphate, chloride, and

TABLE 1.—*Observations and Tests During Seventy-Two Hour Experimental Period*

Procedure	Description	Time Administered Daily
Behavioral ratings by observers		
Estimates of behavior *	25 descriptive items were rated on 4-point scale; these were clustered into 15 categories	12 m., 6 p.m., 1 a.m., 6 a.m.
Estimates of degree of sleepiness	Subjects were rated on a 10-point wakefulness-sleepiness scale	Every 2 hr., 8 a.m. to 12 a.m.
Psychological tests		Every hour, 12 a.m. to 8 a.m.
Estimate of time	Subjects estimated ½- and 2-min. intervals	9 p.m., 3 a.m.
Introspective questionnaire *	A 57-item questionnaire was administered, modified from that developed by Jarvik et al. ⁷ for study of LSD-25 effects; this was clustered into 9 categories	12 m., 6 p.m., 1 a.m., 6 a.m.
Adjective check list *	The list was composed of 106 adjectives descriptive of mental states; these were clustered into 7 categories	12 m., 6 p.m., 1 a.m., 6 a.m.
Drive preference *	Drive preference tests sampled desire for food, sleep, activity, sex, intellectual and hostile behavior: One test was self-rating procedure on a 4-point scale; the other was a forced-choice questionnaire	8 a.m., 4 p.m., 1 a.m., 6 a.m.
Rorschach test	This was a modification of the test designed to identify "psychotic" thinking	2 a.m. (1st and 3d days)
Subjects' estimate of degree of sleepiness	Subjects rated themselves on a 10-point wakefulness-sleepiness scale	Every 2 hr., 8 a.m. to 12 a.m.; every hr., 12 a.m. to 8 a.m.
Fantasy formation	(a) Subjects visualized scenes on blank white cards (b) Subjects remained alone facing wall for 5 min. and then related their thoughts	8 p.m. 4 a.m. (1st and 3d days)
Rate of association to graded nonsense syllables *	Subjects associated to nonsense syllables; speed and ability to perform were measured; the 3 lists were equivalent, but the syllables were different	12 p.m.
Perception of mutilated words (Thurstone's Test)	The capacity to perceive fragmented words was measured	11 p.m. (1st and 3d days)
Learning test-spatial concept formation test ¹⁴	This was a test designed to measure the capacity to organize symbols	3 a.m. (3d day)
Introspective description of experience by subjects	Subjects described retrospectively, after the experiment was terminated, their recollection of the experience	
Endocrinology		
Plasma 17-hydroxycorticosteroids	20 ml. of blood was drawn and analyzed by a modification ¹¹ of Nelson and Samuels' technique ¹¹	8 a.m., 10 p.m., 4 a.m.
Urinary 17-hydroxycorticosteroids	Urine was analyzed by a modification ¹² of technique of Reddy et al. ¹⁴	Every 6 hr.
Urinary 17-ketosteroids	Urine was analyzed by the technique of Callow et al. ¹³	Every 6 hr.

* The results of these tests are expressed numerically in Tables 2, 4, 5, and 6. A scoring system based upon aggregate mean responses for the group of subjects was devised for each procedure. These were inexact measurements but did offer a rough quantitative estimate of the variations in psychological state that occurred during the period of sleep deprivation.

calcium balance, was deprived of sleep for 72 hours and then kept on the same dietary regimen for another five days.

Clinical Observation

Although many patients suffer some degree of insomnia prior to and during an acute psychotic attack, only a few seem to experience prolonged sleep deprivation. The two patients who are briefly described appear to have been cases of this situation. Neither had experienced a previous schizophrenic episode; both were in their middle years, and each had a short-lived psychotic episode that responded rapidly to treatment.

The first patient was a 44-year-old woman who decompensated after the accidental death of her 16-year-old son. While driving the family car, he struck a cow and was fatally injured. For the next 27 hours he lingered in coma and then died. During this time his mother stayed at his side. She cried, remained sleepless, and complained of pains in the region of all her son's injuries. Thereafter she became emotionally more controlled but could not sleep. By Tuesday her insomnia had lasted almost three days, and at that time further evidences of irrationality were present. The next day, after close to 90 hours of sleep deprivation, self-recriminations, and excruciating psychic distress, she became grossly psychotic. She railed against the atomic bomb, expressed religious delusions, refused to wear clothing, screamed, and lapsed into an incomprehensible gibberish. She was taken to the hospital and seven days later, after three electroshock treatments, reverted to normal behavior. Thereafter she received two more electroshock treatments, her behavior remained rational, and she was discharged.

Eight months later, at the time her son would have graduated from high school, a series of events reactivated her psychotic grief reaction. Again she became depressed, ruminative, and intensely miserable; failed to sleep for three days, and relapsed into a psychotic state. She was rehospitalized, was treated with chlorpromazine (Thorazine) and perphenazine (Trilafon) and in six days recovered.

The second patient was a 51-year-old man, a successful cattle and dairy rancher, who had a schizophrenic sister, two years his senior. The previous year he had been elected to the local school board and found himself deeply involved in a dispute as to where a new school should be placed. He represented a minority position and, very much a neophyte to politics, found himself battling the board unsuccessfully. Under the stress

of this bitter conflict, he began to smoke and drink coffee excessively and was so disturbed that he slept no more than two or three hours a night. Finally, after three weeks of turmoil, culminating in four days of total sleeplessness, he became psychotic. He felt that he was being watched, that his telephone was monitored, and became convinced that God had given him special powers. Acting on his newly acquired divine authority, he descended upon the local school and abruptly dismissed the school clerk, superintendent, and janitor. His physician made the diagnosis of schizophrenia and referred him to the hospital. He was placed on a regimen of chlorpromazine, began to sleep again, reduced his consumption of cigarettes and coffee, resolved to leave politics to more skilled and experienced neighbors, and within a few days recovered.

Since patients often unwittingly exaggerate the extent of their insomnia, every effort was made to verify the history in both cases. In the first instance the patient's husband was able to confirm the accuracy of the story, and there seemed little doubt that she had experienced total or near-total prolonged sleep deprivation on both occasions. The second patient had been sleeping in a room by himself, and his wife could not contribute any useful information about disturbances in his pattern of sleep, since she was not present to observe it. There was no way to check his story, except to note that he was an impeccably honest and factual person, ordinarily a good observer, who was convinced that his insomnia had been prolonged and severe.

Experimental Observations on Sleep-Deprived Subjects

1. Psychological and Behavioral Observations.—*A. Intellectual Function:* 1. At 2:00 a. m. on the morning of the first and third sleepless days, all subjects were given a modification of the Rorschach Test,⁸ designed to distinguish psychotic from non-psychotic states. It was assumed that if prolonged sleep deprivation caused a thinking disorder, this would be evident on such a test. All seven subjects scored within the normal range, and variations from the first to the third day were insignificant, indicating that no formal thinking disorder as meas-

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ured by the tests was evident during the testing procedure.

2. On the early morning of the third day, four subjects were given a complex learning test (Spatial Concept Formation Test) that lasted three-fourths of an hour. It called for considerable concentration, the capacity to order symbols, and the ability to integrate and solve moderately difficult problems. As a test, it was the most complex one administered, and intellectually the most difficult we could provide. Nevertheless, at 3:00 a. m., when all were glassy-eyed with fatigue, each subject was able to mobilize his addled senses and concentrate sufficiently to solve the problems. When these scores were compared with those of 53 students who acted as controls, there were no significant differences between the two groups. All four sleep-deprived subjects scored within the normal range.

3. Each day subjects were asked to associate to a list of graded nonsense syllables. This proved to be much too simple a task, and it was accomplished rapidly and efficiently on every occasion. No differences in performance from the first to the third day could be demonstrated.

4. Subjects were given a "mutilated" word test on the first and third days. Again, they performed as capably on the last day as they did on the first.

It was concluded from these studies that subjects deprived of sleep had the capacity to mobilize their intellectual facilities when confronted with these formal tests of relatively short duration. They could perform in a normal fashion under these conditions, despite evidences of disorganization under informal circumstances.

B. Drive States: Subjects were asked to grade their preference for items involving sex, food, sleep, exercise, intellectual activity, and hostile behavior. They were required on a second questionnaire to make a forced choice of these items. Although imperfect procedures, these tests revealed some interesting trends. As might be expected with prolonged sleeplessness, a desire

TABLE 2.—*Drive States*

	1st Day P.M.	3d Day P.M.	1st Day A.M.	3d Day A.M.	
Sex	12	21	20	21	
Food	14	14	14	14	Self rating (7 subjects)
Sleep	7	21	6	21	
Exercise	17	5	14	3	
Intellectual activity	20	2	15	4	
Sex	7	8	9	7	
Food	9	6	10	7	Forced choice (4 subjects)
Sleep	4	12	6	12	
Exercise	6	3	5	3	
Intellectual activity	5	2	7	1	
Hostility	2	3	3	1	

for sleep became prominent, as an interest in exercise and intellectual pursuits waned. Less expected was the persistent and sustained interest in food and sex despite the uninterrupted insomnia, suggesting either that medical students are a hardy breed or that these interests are strong and not easily diminished. Feelings of hostility underwent little change under the conditions of the experiment (Table 2).

C. Estimate of Time: Twice a day subjects were asked to estimate the passage of one-half and two minutes. They were not told at any time how accurately they performed and were asked not to practice. An unexpected observation was the tendency of the subjects to reduce their estimates as sleeplessness progressed. Although one-half- and two-minute intervals were usually judged to be longer periods than those early in the experiment, by the third day most subjects estimated that one-half and two minutes had elapsed before that amount of time had passed. This may have been due to the tendency of subjects on the second and third days to doze, then to awake suddenly and feel more time had elapsed during the "blank" period than really had passed (Table 3).

D. Fantasy Formation: On each experimental day subjects were instructed to stare at a large, white blank card and to visualize a scene. They described the picture, and their comments were recorded verbatim.

TABLE 3.—Estimation of Time*

	Overestimation		Underestimation	
	P. M.	A. M.	P. M.	A. M.
1st day.....	13	20	13	8
2d day.....	8	7	17	21
3d day.....	6	3	12	24

* One-half and two minutes.

The same procedure was repeated a second time, with the suggestion that they visualize another scene. It was noteworthy that these projections remained pleasant throughout the three days. Preoccupations with sleep did not become prominent; scenes did not become closer or more distant; fantasies remained specific and well organized; the number of items stayed virtually constant, and the ratio of human to nonhuman content did not significantly fluctuate from day to day.

In contrast, subjects were asked on the first and third days to sit alone, facing the wall, without conversation for five minutes. Afterward they recorded the thoughts that crossed their minds. This proved to be a much less structured situation. On the first day fantasies were quite specific. They related to thoughts of jobs, girl friends, plans for parties, fishing, and the like. In every case fantasies were well organized and had no obvious reference to the experiment. By the third day the content appeared to have changed. Fantasies frequently pertained to such topics as "cessation of the experiment and sleep" and "How much energy must be expended on keeping awake even for this five minutes of reverie?" "What do all

these tests mean?" "Why doesn't Russia conquer Finland?" "the cycles of sleepiness," and similar preoccupations. Many fantasies dealt with the immediate dilemma of sleeplessness and the problems it provided. Several subjects noted that their thoughts were jumbled, and that they "couldn't think of anything for more than 10 seconds," or that they "had difficulty concentrating." The two techniques indicated the dichotomy between performance on a specific test and mentation during periods of informal behavior. On the first test responses were logical and organized; on the second procedure, after prolonged wakefulness, thinking tended to be loose and at times befuddled.

E. Periodicity of Sleepiness: A characteristic of prolonged wakefulness which has been noted by others, and that was clearly demonstrated, as well as reported, by our subjects, was the rhythm of sleepiness. There were two general patterns. One was the usual diurnal pattern of alertness during the day and early evening, followed by somnolence at night. The other involved short periods of an hour or two, usually during the earlier hours of the morning, when fatigue became virtually intolerable.

The broad pattern is illustrated in Figure 1, where the consolidated estimates by subjects of the depth of sleepiness during the vigil are plotted. Estimates by the observers followed the same general pattern. Generally, subjects tended to be less sleepy during the hours they were accustomed to be awake and more somnolent late in the evening and

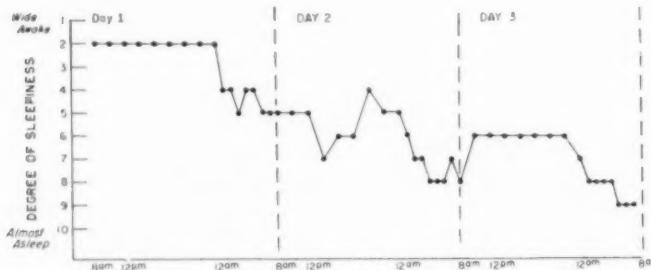


Fig. 1.—Average degree of somnolence as estimated by the six subjects during the three days of wakefulness.

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early in the morning, when they habitually slept. Although they were quite alert during the first day, with each succeeding day, as well as night, there was increasing fatigue, so that on the third day they were sleepier than on the second day. Most had little trouble during the first 24 hours. It was only the last two days that vigilance and activity were necessary to forestall sleep.

Interpolated throughout were waves of sleepiness. One subject described them as lasting for one and one-half to two hours at a time. Between them he would feel fairly normal. His worst periods would occur at 5:00 or 6:00 o'clock in the early morning. Another subject experienced his first wave at 10 p. m. on the second day. This lasted only 45 minutes, and he remained alert until 4 a. m. that morning, when he was overwhelmed by a period of painful somnolence, which lasted two and one-half hours. At 10 p. m. on the evening of the third day, and also from 2 to 7 a. m. the same day, he had similar experiences. A third subject felt a little sleepy around his usual bedtime at midnight the first day. At 4 a. m. to 5 a. m. the first morning he had his first strong wave of sleepiness, which lasted two hours. He then became awake and felt almost as though he had had a night's sleep. From 2 to 6 a. m. the second day he again found it difficult to remain awake, but by 7 a. m. he was again alert. At 2 a. m. on the third day his drowsiness became severe. He stated: "I was very tired—this was not the tired feeling after a long day's work at physical labor, but the tired, nagging, feverish feeling of being just all run down. I was very drowsy, and nothing but very active play or moving about kept me from nodding away." The state of extreme drowsiness persisted until 7:30 a. m., when it began to lift.

The other subjects had similar experiences. It was surprising to observe how the psychobiological pattern of the sleep-wakefulness cycle persisted despite the unremitting, abnormal 72 hours of sleep

deprivation. During the early hours of the morning, when sleep was habitual, sleepiness was most intense and the difficulty of remaining awake was severest. By 8 or 9 a. m., when all were accustomed to being awake, all felt considerably more alert, and there was a marked diminution in somnolence, even after three days of sustained wakefulness.

F. Visual Changes: All subjects experienced some visual distortions, ranging from minor disturbances to hallucinations. During the early morning of the third day, one subject felt that the men's room seemed larger and the floor higher. The dark squares of the floor tile seemed to pulsate and would become darker, as well as larger, with every pulsation. A little later, he reported that the floor of the laboratory "seemed to be covered by a layer of shimmering water. I knew the hallway doors should be familiar but they looked strange." It looked as though the room were on a second story, and it appeared to him that it was necessary to climb a step to get to it from the hall. He commented that late the second evening "as I walked down the hall, I thought I saw an old lady sticking her head out from the room. She seemed to have gray hair, which was rather 'frizzy.' I stopped to look again. She still had her head showing, and it did not move. It wasn't until about 10 yards from her that I realized it was a fire alarm box." He also saw a fine smoke coming from the linoleum floor cover as he was finishing his breakfast. The smoke then began to rise from the floor in a very fine stream. This became misty and faded into a fine spray of water, so that as he stared at the floor more closely, fine jets of water appeared to be rising.

One subject occasionally had the sensation of tunnel vision, and another one saw things shimmering and oscillating. He perceived the "coke" machine as moving up and down. Another subject on the second night spent considerable time pacing the hall. Momentarily, he saw a roll of luminous

chicken wire on the floor, and, as he walked through it, the wire disappeared and did not return. For a period, the base of the shuffleboard stick seemed to follow an undulating, twisting motion, although it was well lighted and only a few yards away. The legs of a table also occasionally quivered. One subject reported that during the third night the "coke" machine became distorted, as though he were looking at it through a piece of glass with flaws in it. He also saw black spots in the periphery of his visual fields.

G. Auditory Changes: Subjects reported that loud sounds seemed harsh and disrupting or that people's voices seemed distant. One noticed that he could watch his companions' mouths as they talked next to him, yet feel their voices were coming from the next room. Another described it as though "their voices seemed to come from somewhere else." During periods of somnolence, all found it difficult to concentrate on conversations and to listen intelligently. They might talk or listen and then be unable to remember the content of the conversation. None experienced frank auditory hallucinations. One commented that the radio was on nearly all the time; yet occasionally, he would notice that he had not heard the music for an hour or more.

H. Paresthesias: All subjects reported some variety of altered sensation. Like so many other experiences during the procedure, these sensations also were usually transient. One felt his body was numb and insulated; his eyes smarted, and his muscles felt stiff and sluggish. He compared the sensation of numbness and feeling of insulation with that of a mild alcoholic intoxication. Another was walking down the hall when his left heel seemed to raise by itself, and a "funny," electrical, cold sensation shot up the back of his leg. He experienced, also, a peculiar numb feeling in his knee, a fleeting flush over his skin, and peculiar feelings in his hands.

Another subject felt a tight sensation over his face, similar to those he had ex-

perienced previously with alcohol and lysergic acid diethylamide. One reported that his hands seemed to be larger, and another had a warm, tired feeling in his arms and legs. Only one subject had persistent sensory disturbances. He had a "creepy" hypersensitivity all over his skin, except for his palms and soles, that was constant and lasted throughout the final 48 hours of sleep deprivation.

I. Mood Changes: The setting of the experiment was uncritical and friendly. Everything was done to minimize anxiety and reduce irritations. The investigators were casual and amicable, and the entire procedure was an informal one. In this specific setting disturbances in mood, particularly unpleasant reactions, were infrequent. Two subjects reported periods of anxiety—one because he was concerned about his ability to stay awake during the second day, and the other, due to his concern about feelings of depersonalization and a progressive sense of loss of self-control. Several passed through periods of giddiness and silly laughter, like addled drunks, when their behavior became uninhibited. One moved through several stages. Until 45 hours had elapsed, he was happy and silly. Thereafter he felt rather depressed, enough so that a slight irritation could have provoked an argument or fight.

J. Impaired Cerebration: Although the subjects could mobilize their befuddled faculties for specific, formal psychological tests and perform normally under pressure, their informal behavior reflected intellectual deterioration. They behaved and felt impaired, particularly during the later portion of the experiment.

One expressed it: "There was extreme difficulty keeping my thoughts coherent. On one occasion I remember writing out a profound statement and ending the statement with the irrelevant comment, 'owes \$8.00.'" Some had difficulty in forming their thoughts, in finding the proper words, or in composing a sentence. They forgot their fellow-participants' names, and one

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had the nagging conviction that Ronald's (another subject) name was really not Ronald but Robert. There was confusion as to what they had said in casual conversation and what others had said to them. One recalled that they had played Scrabble and said: that "An 8-year-old boy could have doubled my score. Most of the words I put down were two letters, such as 'at, do, it.'" Most periodically felt confused. Thoughts were often jumbled, and certainly during the last evening thinking was fragmented during periods of inactivity. One subject recalled trying to discuss women with a fellow subject. It must have been a fascinating conversation, since neither was able to follow the thread of the discussion.

K. Miscellaneous Observations: One subject who had a mild cold noticed it

TABLE 4.—*Adjective Check List*

Categories	First Day P. M.	Third Day P. M.	First Day A. M.	Third Day A. M.
Alertness	53	10	20	5
Feeling of well-being	78	24	35	15
Emotional distress	1	7	2	10
Hostility and irritability	6	8	3	3
Disorganization in function	2	1	5	27
Sleepiness and fatigue				
Mild	5	40	35	40
Severe	1	10	7	15
Increased motor activity	10	30	30	20

became worse during the period of sleep deprivation. Two others developed colds during the experimental period. In all three cases the upper respiratory difficulties cleared after the subjects finished the marathon and had ample sleep.

Two subjects noticed some motor incoordination, unsteadiness, and ataxia, comparable to the feeling of being intoxicated. Several reported "waking" dreams, when they might stand or sit with eyes open and yet be completely out of contact, experiencing sensations like hypnagogic reveries.

Time seemed to several to be a "hodge-podge." One felt the hours passed rapidly

TABLE 5.—*Introspective Questionnaire*

Categories	First Day P. M.	Third Day P. M.	First Day A. M.	Third Day A. M.
Motor incoordination	0	10	0	60
Feeling of weakness	3	60	23	87
Sleepiness	20	100	90	130
Blurring of vision	0	45	0	70
Illusions & hallucinations	0	15	0	10
Paresthesias	0	20	5	20
Emotional lability	0	7	10	30
Impaired concentration	10	110	20	110
Feelings of estrangement	0	20	0	50

but that the days were interminable. Another stated that between activities time seemed to stand still.

A variety of sensations that could be subsumed under the heading of depersonalized and derealistic states were reported. There were reports of feeling "separated from others." One subject stated that for about five minutes he pondered whether the whole experiment were a dream. Most felt moments of estrangement, distance from others, and disturbances in their habitual concept of their person.

Much of the preceding descriptive material is summarized in Tables 4, 5, and 6. These represent quantitative estimates of behavior, affect and thinking during the three days of the experiment and are analyses of the adjective check list, introspective questionnaire, and the observations by the monitors.

TABLE 6.—*Observations by Monitor*

Description of Subjects	First Day 1 A. M.	Second Day 1 A. M.	Third Day 1 A. M.
Sad	0	0	0
Asocial	0	0	0
Emotionally disturbed	0	0	0
Withdrawn	0	0	0
Angry	0	0	2
Happy & friendly	8	7	7
Anxious	0	0	2
Apathetic	0	0	7
Alert	9	7	2
Social	10	7	5
Sleepy	1	5	9
Restless & moving	2	4	6
Thinking clearly	9	8	2
Thinking "fuzzily"	0	2	9
Acting drugged	0	5	12

TABLE 7.—Plasma Adrenal Steroids—
Hydrocortisone*

	8 A. M.	10 P. M.	4 A. M.	
Day 1	13	15.1	0.5	2.2
	11.6	17.8	3.0	0.8
	12.4	12.4	1.2	3.0
	16.4		1.7	7.0
Average=14.1		Average=1.8	Average=4.7	
Day 2	9.6	10.3	1.4	2.2
	11.3	21.4	2.8	1.8
	10.6	18.8	1.8	2.4
	10.8		4.0	7.8
Average=13.3		Average=2.3	Average=5.8	
Day 3	9.3	15.8	1.2	2.3
	11.8	14.2	3.1	2.2
	10.0	18.3	1.8	3.6
	11.4		4.3	9.0
Average=13.0		Average=2.6	Average=6.6	
Day 4	10.3	13.9		
		17.0		
	9.2	16.0		
Average=12.9				

* Micrograms per 100 ml. of plasma.

II. Adrenal Steroid Studies.—In agreement with the observations of previous investigators,^{15,16} we found no significant alterations in adrenocortical activity despite 72 hours of wakefulness. Both the concentrations and the diurnal rhythm of hydrocortisone (17-hydroxycorticosterone) in the blood remained remarkably stable and normal from day to day (Table 7).

Similarly, the 24-hour urinary excretion of the 17-hydroxycorticosteroids and the 17-ketosteroids remained relatively constant from day to day, and the normal urinary diurnal rhythm of the 17-hydroxycorti-

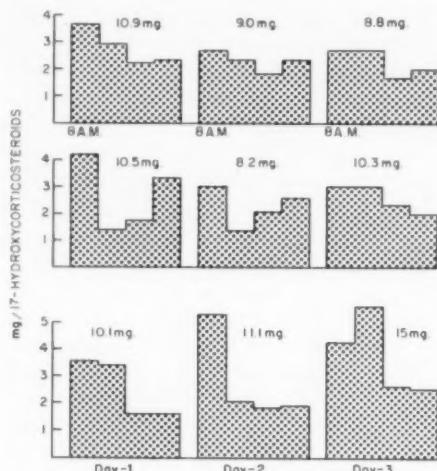


Fig. 2.—Urinary excretion of 17-hydroxycorticosteroids. In all subjects, during the period of sleep deprivation, urinary collections were made every six hours. These aliquots were analyzed, in three subjects, for 17-hydroxycorticosteroids, and demonstrated the persistence of a normal diurnal rhythm.

costeroids persisted (Fig. 2). This constancy appeared to be a tribute to the body's capacity to maintain its normal biological patterns despite a radical departure from accustomed routines.

III. LSD-25 Experiment.—Four subjects were chosen for this experiment. All had received lysergic acid diethylamide (LSD-25) without sleep deprivation on at least four previous occasions, so that their responses to the drug and tolerance for it were well known. Each had taken 0.5 µg. of LSD-25 per kilogram of body weight

TABLE 8.—Dosage

Sub- ject	1 µg./Kg. LSD-25 with Other Drugs	1 µg./Kg. LSD-25 with Other Drugs	0.5 µg./Kg. LSD-25 with Other Drugs	0.5 µg./Kg. LSD-25 with 48 hr. Sleep Deprivation
B	Hallucinations	Hallucinations (mesca- line 0.1 gm.)	No hallucinations	No hallucinations (amobarbital sodium 0.3 gm.)
S		Hallucinations (amobarbital 0.3 gm.)	No hallucinations	No hallucinations (atropine 1.2 mg.)
M		Hallucinations (BOL 2 mg.)	No hallucinations	Hallucinations (mescaline 0.1 gm.)
R	Hallucinations		No hallucinations	No hallucinations (BOL * 2 mg.)

* BOL 148 is 2-bromo-d-lysergic acid diethylamide.

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alone or in combination with another compound on two or three previous occasions and had not developed perceptual disturbances (LSD-25 hallucinations) except in one instance, when 0.5 μ g. of LSD-25 had been combined with 0.1 gm. of mescaline. In contrast, all subjects had hallucinations after taking 1 μ g. of LSD-25 per kilogram of body weight¹⁷ (Table 8).

After being deprived of sleep for 48 hours, each subject received 0.5 μ g. of LSD-25 per kilogram of body weight. In striking contrast to previous responses, all four under the combined influence of sleeplessness and drug, developed hallucinations. It should be reemphasized that this amount of drug had not previously been hallucinogenic. Furthermore, the total response to 0.5 μ g. of LSD-25 per kilogram combined with sleep deprivation was in other particulars as severe as or severer than the reaction to 1 μ g. of drug per kilogram in the rested state.

It would appear from these observations that sleep deprivation enhances the disruptive effects of LSD-25 upon ego function. Presumably, this may have been due to an alteration in cerebral metabolism consequent to prolonged sleeplessness, which made the brain more susceptible to the "psychotomimetic" effects of LSD-25.

IV. Metabolic Study.—The one subject who was studied on a metabolic ward showed no significant changes in the urinary excretion of chloride, sodium, potassium, calcium, phosphate, or nitrogen during the 72 hours he remained awake, as compared with the seven-day control period preceding the sleep deprivation and the five-day control period which followed. The only unusual observation was a polyuria of 5000 to 6000 ml. during the test period. It seemed unlikely that this might have been due to a posterior pituitary inhibition, since our other subjects did not have high 24-hour urinary volumes. The study did indicate that sleep deprivation of this magnitude neither increased protein catabolism nor disturbed electrolyte metabolism, and the results

were consistent with our observation of a lack of variation in adrenocortical activity.

Comment

It has long been recognized by experienced inquisitors in "police" states that sleep deprivation can induce personality disorganization. They have been well aware that enforced wakefulness, when combined with emotional turmoil and physical isolation, may lead to psychotic behavior in susceptible subjects.¹⁸ These are observations that have generally been overlooked by the psychiatrist.

It is our impression that these unconscionable techniques are unwittingly reduplicated by certain psychiatric patients who experience intolerable psychological distress and then suffer emotional isolation and prolonged sleeplessness. In a few susceptible persons the combination of these forces may precipitate some schizophrenic illnesses. Two examples were cited of patients who illustrated this situation. Both were racked with intense psychological pain and overwhelmed by seemingly insoluble problems. Both failed to sleep for several days, emotionally isolated themselves, and became psychotic. In each case the schizophrenic episode was brief and rapidly reversible. Either might have become schizophrenic without the additional insult of sleep deprivation, but it seems plausible that the insomnia may have been a critical factor in the process. Since these clinical situations combined a variety of noxious influences and did not allow an accurate estimate of the impact or importance of the individual factors, one of the disturbances—the loss of sleep—was isolated and investigated in experimental subjects. The setting of the experiment was a social one, in which communication was free and congenial. This eliminated in part the factor of isolation. Furthermore, every effort was made to create and maintain an anxiety-free situation so that emotional disturbances could be minimized or excluded. This left a relatively controlled situation, where the prin-

cipal variable was prolonged wakefulness. In this setting subjects remained awake for 72 hours, and series of observations and studies were performed.

After prolonged sleeplessness subjects were able to handle relatively brief psychological tests adequately, but developed a variety of ego disturbances during the intervening periods. These disturbances included feelings of depersonalization, confusion, hallucinations, paresthesias, motor incoordination, and other subtle psychological changes. All of these characteristically were inconstant and came in waves, coinciding with periods of intense somnolence. They probably represented hypnagogic states when the subjects were "asleep on their feet." No subject became psychotic. One can only infer that if these changes were to occur in someone who was also profoundly anxious and deprived of group support, more serious psychopathological sequelae might result.

A second series of observations in which LSD-25 was combined with sleep deprivation had further interesting implications. The hallucinogenic properties of the drug were considerably enhanced by sleeplessness. Amounts of the drug which ordinarily produced mild changes induced extensive perceptual disturbances in subjects who had been awake for 48 hours. This suggested that the loss of sleep may have altered cerebral metabolism so as to make the cortex more susceptible to the hallucinogenic properties of the drug.

Another general observation was the stability of deeply entrenched biological rhythms. Despite continuous wakefulness, both the diurnal sleep-wakefulness pattern and the adrenal steroid pattern followed their normal fluctuations, and protein and electrolyte metabolism remained unaltered. None were significantly altered by the extraordinary circumstances of the experiment.

Unfortunately, the observations to this point are suggestive but not conclusive. The facts suggest, however, that prolonged sleep deprivation may have a pathogenic potential,

especially when combined with other disruptive psychological processes, and that prolonged wakefulness may be a critical factor in the precipitation of a few schizophrenic illnesses.

Summary

The clinical observation that a few schizophrenic episodes are preceded by prolonged insomnia led us to postulate that sleep deprivation, although a consequence of the emotional turmoil, might play a critical role in the precipitation of some psychoses. Therefore, studies were made of normal subjects who were kept awake for 72 hours. The setting was a social one, where anxiety was kept minimal. Changes on psychological tests were insignificant, but behavioral and subjective alterations were considerable. Feelings of depersonalization, illusions, hallucinations, disturbances in time perception, and auditory changes were common. Despite the long period of wakefulness, adrenocortical activity remained normal.

In another study subjects were kept awake for 48 hours and then given small amounts of LSD-25. Sleep deprivation markedly enhanced the ego-disruptive effects of the drug. It is suggested that sleep deprivation, when combined with isolation and incapacitating anxiety, may have a pathogenic potential that has not been adequately appreciated.

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Suicide, Menticide, and Psychic Homicide

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Original sin is using empathy
not for sympathy but for antipathy.

In this clinical study I wish to call attention to the crime of psychic homicide, which is usually committed as a crime by omission. It is only within the last few years that I myself realized how some suicide victims are unwittingly propelled into the act.

The act of suicide is always committed in relation to fellow beings. However subtle and unconscious this relation may be, other people play a role in the sum total of motivations of those who commit the final deed. That is why the bystanders are afraid of suicide, and why it is in some countries a legally punishable act—as, for instance, in England—because the self-chosen death burdens the other man's conscience.

Psychiatrists agree that punishment of parents or spouses or bosses is one of the most frequent motivations of suicide. This form of mental blackmail may be conscious in the suicide-candidate or can be more subtly hidden behind many rationalizations. It is a fact that loss of pride and self-esteem and the fantasy of the future remorse and mourning of those to be punished play an important role in the motivations. The person who commits suicide hardly ever kills himself—as an individual, independent entity—but mostly kills in effigy those he identifies with and depends on. The murderous fantasy usually remains unconscious. In such a case suicide may become a liberation—albeit an ultramasochistic one—from an obscure identification with a hostile person, and I have seen cases in which “attempted” suicide initiated the crisis of breaking away from a dependency.

Others committed suicide because they were inadvertently aware of the wish or the command of their proxy that they had to

die, though this “homicidal” verdict had seldom been verbalized in a conscious way.

It is not my aim here to describe the various motivations of suicide. I want, however, to ask attention for a form of psychic murder—as it occurs not infrequently—with its general implications for human relations and human responsibility. Those who push others into suicide are legally not held responsible, as yet. A good doctor-patient relation can be very protective in case of meditated suicide, but it can also be dangerous if the value of the therapeutic transference is not understood.

CASE 1.—A husband tried to remedy difficult marital relations by soothing his wife with tranquilizers and sedatives. In the meantime he went on with his extramarital affairs. When, finally, his wife took an overdose of barbiturates and was transported to a hospital, he broke down and sought psychiatric advice for himself. In a nightmare, he told me he was at the burial of his wife—who in reality did not die—and he was so sad that he fell down with a heart attack. This rather simple case of death wish and punishment brought both husband and wife into treatment. They finally were divorced, and both got a better chance with new partners after they had finished their treatment.

CASE 2.—An engineer, struggling all his life with a harsh, domineering, and alcoholic father, gave his father during his last visit a bottle of barbiturates to “cure” his addiction. He was very well aware what he expected his father to do. When two days later the telegram came announcing the suicidal death of his father, he drove home at a reckless speed, however without killing himself. Only after having gambled away his father's money did he come into treatment, but he was never willing to face his psychic murder.

CASE 3.—A doctor having an affair with his secretary denied his wife the treatment by a colleague for her reactive depression. Finally he took a vacation with his secretary and his little daughter (his only child), leaving his wife alone at home. After two days she committed suicide on his unconscious command. The husband remained unaware of his psychic murder.

Submitted for publication July 29, 1958.

SUICIDE, MENTICIDE, AND PSYCHIC HOMICIDE

CASE 4.—A depressive patient has for years been in treatment in an analytically oriented form of psychotherapy. Finally the therapist broke the relationship because the patient was not able any longer to meet his fee, at which the patient promptly reacted with a suicide attempt. The relation with a new therapist on a more economical and less frequent treatment basis brought out the masochistic dependency on the former therapist and her translation of the therapeutic rejection as "drop dead."

CASE 5.—An alcoholic student was brought by his domineering and hostile mother to the therapist to be cured of his addiction. Three months later, at Christmas, his mother sent him a case of whiskey as a present for the holy season. Happily enough, the patient was able to understand his mother's inadvertent command, and this became the first real asset for the therapy.

All this sounds like a cynical summing up of unconscious death wishes we so frequently detect in psychotherapeutic practice. Usually, the acting out is not so obvious as that in the examples mentioned.

The burden of inadvertent hostility and murderous wishes pushing those with weaker egos into depression and suicide is, however, frequently seen. Especially in suicide by children we realize how much rejection, teasing, and vituperation have to do with loss of self-esteem, and how these humiliations can drive the young person to suicide.

In 1951, I described the crime of menticide,¹ now also called brainwashing, as the organized system of political and psychological intervention and judicial perversion, in which a powerful tyrant synthetically injects his own thought and words into the minds and mouths of the victims he plans to destroy by mock trial. By first pushing the victim into abject dependency, and by then filling the grooves of the inner gramophone record, man can be conditioned and coerced into doing and confessing nearly all his inquisitor has imprinted onto his mind.

Since then it has become more obvious that the concept of brainwashing and thought control goes much farther than the utter mental submission of an individual. Entire communities can be subjected to mental pressure and mental coercion, as

we see in the cold war and in political campaigning. In everyday life an unobtrusive mental coercion exists by reason of factors nearly unexplored. The changing pressures of a world in social and technical revolution make man's ego more vulnerable.²

It is here that psychiatry took the lead. It could show how subtle, unaware attitudes of parents and environment change the behavior of the child. The molding of the youngster takes place through a group of factors and challenges, most of which we are just beginning to explore.

I now want to go back to my old theme of psychic homicide, asking what hostile factors are inadvertently picked up by the child or the adult in increased mental dependency.

CASE 6.—A borderline schizophrenic mother, never wanting to have a child, gave birth, nevertheless. From the very moment of birth the child refused to take any food (breast, bottle, or solid food) from the mother, but accepted it from anybody else.

Although the mother woed the child all the time, the child reacted immediately to the unconscious death wishes of the mother (known to me from a former treatment). Finally, we had to separate mother and child for the first three years to make the world tolerable for both mother and child.

Such unconscious attacking of each other, through which one person submits to unconscious intentions of the second person (the proxy or identification), often causes the committing of suicide of one to obey the other. This is most clearly seen in the symbiotic relationship between the omnivorous latently psychotic mother and her child. We may say that nearly every act of such a child is done in relation to an unconscious directive of the mother, and vice versa.

CASE 7.—In one such dramatic battle, the daughter, a mathematician, tried repeatedly to get away from her widowed mother. Although the daughter taught at the local high school, she could never go very far away from her mother. Yet when her mother had to make a trip, she, the only child, usually became sick. Their everyday relation was a continual mutual vilification, alternating with loving remorse. When, finally, the daughter planned to go on vacation, the mother threatened with suicide; and when the mother was away, the patient became more accident prone. Her mother

used all the usual means of mental attack to keep the daughter in her grip: vilification, writing anonymous letters, lobbying, urging other people to suggest ways to keep her daughter with her, isolating the home from friends, crushing her daughter's ego continually. The mother's justification was always her fantasy about her daughter's poor health.

When, finally, the daughter succeeded in going away from home alone on a vacation—after a long struggle in psychotherapy—the mother committed suicide. Then it took a long time to overcome the daughter's mournful identification with the dead proxy and her guilt of psychic murder. The growing awareness of her mother's ambivalence and how her mother had tried to kill her mentally, helped the daughter to find new, more creative and freeing identifications.

Conclusion

The act of suicide is not only a form of mental blackmail, with the unconscious idea of punishing a disappointing relationship; it may also be the follow-up of a command

and verdict of a proxy, a person the victim identifies with. Several examples of psychic homicide are given. The act is legally not punishable yet. I relate it to my former concept of menticide. The existence of mutual mental coercions can push people consciously or without awareness into irresponsible and immoral acts.

In the age of encroaching technology and growing community pressure, resulting in weakening ego, decreased self-esteem, and diminishing personal responsibility, these unconscious attacks on a person's will and integrity become more and more relevant.

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Study of a New Schizophrenomimetic Drug—Sernyl

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Introduction

The production of model psychoses has been employed as a technique for testing hypotheses relevant to the causes, correlates, and treatment of schizophrenia since 1921, when De Jong demonstrated experimental catatonia by giving bulbocapnine to animals.⁵ This method of study has received considerable impetus with the discovery of the hallucinogenic properties of lysergic acid diethylamide (LSD-25)²² and other psychotomimetic agents.

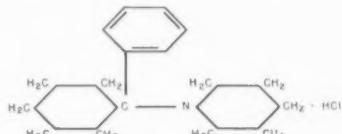
Objections have since been raised to the drawing of premature analogies between the psychotic-like states produced by drugs and the psychopathology of schizophrenia. Ebaugh has pointed out that "the difference between these pseudopsychoses and schizophrenia is so striking that such experimentation seems to have only tenuous relevance to the problem of schizophrenia."⁷ On the other hand, Wikler has asserted that "from the standpoint of the development of dynamic (causal) concepts about human behavior, it matters little whether or not model psychoses resemble schizophrenia. Drugs which modify sensing, feeling, wishing, ideating, etc., can be used as tools to detect and manipulate the biochemical, physiological, and psychological variables that regulate these functions."²³ We assume that availability of laboratory techniques for inducing psychotic behavior portends the accelerated development of control over the basic biopsychological processes implicated in the psychoses.

Submitted for publication July 17, 1958.

Parke, Davis & Company supplied the Sernyl used in this study.

From the Lafayette Clinic and Wayne State University College of Medicine.

This report describes the schizophrenic-like behavioral effects of Sernyl, a new drug chemically unrelated to other psychotomimetic agents and with unique neuropharmacologic properties. Sernyl, 1-(1-phenylcyclohexyl) piperidine monohydrochloride,³ is one of a class of sensory-blocking agents recently developed for anesthesiology (Figure). Griefenstein et al.



Structural formula of Sernyl.

have used it in this way with 41 patients and believe that its action is unlike that of any other known anesthetic.¹² It produced complete analgesia; yet patients were still awake, with eyes open. Sernyl became of psychiatric interest when Meyer, Griefenstein, and DeVault observed the postoperative development of transient psychotic states.¹⁶

The sites of action of this drug in the central nervous system have not been identified. As judged by the clinical observations of Meyer, "the drug is presumed to have a relatively selective action on thalamus and mid-brain, resulting in demonstrable impairment of pain, touch, proprioception and discriminative aspects of sensation."¹⁶ Motor function is relatively unimpaired until with large doses ataxia, rotatory nystagmus, and bilateral ptosis result. Domino, in preliminary studies, reported: "In unanesthetized beagle dogs and Macaca mulatta monkeys with chronic electrode implants, variable effects on the cortical EEG were obtained, depending upon the dose of

Sernyl administered and the individual animal. These effects varied with increasing dosage from minimal to no change in the EEG, to medium-voltage fast waves, to high-voltage delta activity. Photic-driving responses were decreased in amplitude, as were electrical discharges synchronous with respiration recorded in the olfactory bulb and medial amygdala.⁶

The purposes of the present report are (1) to describe the sensory and cognitive deviations produced by the drug; (2) to compare these deviations with schizophrenic symptomatology; (3) to propose a hypothesis concerning a mechanism which may be operative in both the model psychosis produced by Sernyl and certain symptoms of the schizophrenic process.

Method

Nine normal subjects and nine patients were selected for this study. The normal subjects included six medical students, two residents in psychiatry, and one attendant. Four patients were suffering from chronic schizophrenia, with illnesses of 8 to 10 years' duration, and one was an acute catatonic schizophrenic ill for four months. Of the remaining four patients, two had "pseudoneurotic" schizophrenia, while the other two had character disorders with neurotic features.

Sernyl was given intravenously in a subanesthetic dose of 0.1 mg. per kilogram in 150 cc. of 5% dextrose over a period of 12 minutes. Marked reactions to the drug began in three minutes and usually persisted up to one hour. During this time the subjects were interviewed, given selected psychological tests, and evaluated neurologically. A continuous recording of the content of each interview was made. Tape recordings and stenographic records were used. In addition, some nonpsychotic subjects wrote retrospective accounts of their drug experiences. The patients were kept under daily observation following drug administration to record any changes in behavior.

Results

The general psychological effects of Sernyl on the normal and patient groups are summarized in the accompanying Table.

Psychological Changes

Body-Image Changes.—Alteration in body image was the earliest and most characteristic reaction to the drug. It was reported

Incidence of Sensory and Cognitive Deviations Produced by Sernyl in Normal Subjects and Patients

Deviations	Percentages	
	Normals (N=9)	Patients (N=9)
Body-image changes	100	100
Estrangement	100	100
Disorganization of thought	100	100
Negativism and hostility	67	67
Drowsiness and apathy	100	100
Hypnagogic states	56	33
Feelings of inebriation	78	22
Repetitive motor behavior	29	44

clearly by all 16 subjects who were able to communicate adequately. The remaining two subjects were chronic schizophrenics who were unable to provide definite information as to their subjective states under the drug. The body-image disturbances were accompanied by a loss of "ego boundaries," impaired ability to distinguish between self and nonself stimuli, feelings of depersonalization, and a sense of unreality.

A normal subject reported: "I feel far away; now I'm coming back. My arms and legs feel distant." A medical student in recall stated: "Before I realized it, I was standing, but I didn't feel like I was standing. I didn't know where my feet were, and I didn't feel myself get up. I know I got up fast because my body felt light, just as though my legs didn't have much to support. When I began to walk, I didn't know where my feet were. I could feel my shoes on my feet, the pants around my legs, a slightly numb sensation like that in my arms, but I couldn't feel them move."

Another nonpatient subject stated: "My arm feels like a 20-mile pole with a pin at the end." The experience of floating "in and out, up and down," together with feelings of flying, was repeatedly described. There were prolonged sensations of subjective vertigo, associated with alternate contraction and expansion of body size. There were feelings of "selflessness" of not being human, and of being an "empty nobody." "I am a small . . . not human . . . just a block of something in a great big laboratory."

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A disturbing sense of unreality accompanied the body-image distortions. TAT cards became "real," and some subjects literally attempted to relate themselves physically to the figure in the picture. One male patient became enraged at the young man in Card 6BM and belted the card across the room. In response to TAT Card 13MF, which depicts a standing male figure and a woman lying with breasts exposed, he remarked on the woman's sadness and cradled the picture in his arms while uttering soothing phrases.

Estrangement.—There was a commonly experienced profound sense of aloneness or isolation. The sense of being completely detached from all environmental objects and tensions was reported by several subjects directly, and implied by others who were not able to verbalize so clearly. This experience involved a sense of loneliness, but was not always accompanied by fear or anxiety. While the experience was a strange one for the subjects, they sometimes appeared to become passive and relaxed.

The loneliness was sometimes accompanied by an intensification of dependency feelings. There was a desire for the presence of a supportive figure, with indications of rejection-sensitivity and resentment when the subject was left alone by the experimenter.

A normal subject became angry when he was left alone in the experimental room. He stated reproachfully, when the examiner returned: "I trusted you and then you left me alone. Why did you leave me? I should have brought my wife along." Another normal subject, as he was recovering from the effects of the drug, described feeling as though the examiner were at a "great distance" from him. A normal subject, who wished to be left alone to sleep when the drug was wearing off, still preferred that the door to the experimental room be left open.

Disorganization of Thought.—Consistent deficits in the organization and direction of thought was a marked attribute of the drug state. This was seen in all subjects. Most

striking was the inability to maintain a set, frequent loss of goal ideas, and impairment of the "abstract attitude." Some subjects showed blocking, neologisms, word salad, and echolalia. The subjects appeared to be struggling to describe feeling states which they were unable to define except in fragmentary phrases. To obtain information at the height of the drug effects, the examiner was forced to ask extremely simple and direct questions.

Proverbs were interpreted in a fragmentary, concrete manner, or were simply repeated as though this implied meaning. Without the drug, in response to "a drowning man will clutch at a straw," a subject responded: "A person who is desperate will grab at anything regardless of its value to him." In the drug state, he answered: "I think it is—a drowning man . . . will clutch at a straw. It means a drowning man will clutch." The loose and asyndetic quality of thinking is illustrated by the following response to TAT Card 8BM: "Oh, there is a doctor and a surgeon and a boy and a gun and a boy, boy, boy, boy, boy, boy, knife, gun, man, card, surgeon . . ." The performance of serial 7's became an impossible task for most subjects.

Negativism and Hostility.—These reactions were seen in many subjects. Oppositional behavior was observed, varying from subtle expressions of hostility, in the more sophisticated subjects, to child-like negativism and catatonic-like reactions, in more naïve and characterologically immature patient subjects. One medical student, while in the recovery phase, told of his feelings of futile anger. He felt hostility toward the examiner, but was completely impotent to express it. A passive-aggressive man became stubborn and resistive to instructions. He held his eyes tightly closed and pursed his lips, refusing to attend to tasks in which visual signals and verbal responses were required. Subjects often responded with a "no" when asked if they could hear.

Drowsiness and Apathy.—All subjects exhibited progressively increasing drowsi-

ness. At times, some appeared to fall asleep but remained immediately responsive to questioning. In their retrospective accounts, they recalled being able to hear questions and instructions and to comprehend what was expected of them, but felt no special compulsion to comply with the examiner's requests. They verbalized this as an "I don't care" attitude. Their appearance, especially toward the latter stages of the examination session, became more and more strikingly apathetic.

Hypnagogic State.—These phenomena were reported both by patients and by normal subjects. These were dream-like productions, which occurred in a waking state and which usually had a basis in the subject's past. The subjects reported feeling as though they were in some specific setting and were able to describe it in detail. While the reports typically had reference to past events, they were expressed as though the experiences were taking place at the moment. The lack of time-boundedness was reminiscent of dreaming. As in dreams, multiple shifts occurred in the settings experienced by the subjects, sometimes in rapid succession.

A pseudoneurotic schizophrenic male patient reported that he was "in a swing," which he proceeded to draw for the examiner. Shortly thereafter, he stated that he was in his third-grade classroom, which he described elaborately, including the recognition of an old friend in the classroom. At another time, he felt that he was on his ward, and was able to enumerate and point out the locations of various objects there.

In each of these experiences, the subject responded as though he were an integral part of the perceived setting, rather than an observer of detached, projected images. Insight into the unreality of these perceptions was sometimes clear, and at other times vague. In his retrospective account, a medical student subject formulated his impression of this type of experience vividly. He reported: "I was afraid at the height of these experiences that this would never end, and this was me as I always was and

always would be. I felt as though I was in the midst of a horrible and dreadful nightmare, to compare it with something I've experienced before. The walls at times became long, and I thought I was walking through a long corridor. I thought of where I was, in the heart of Detroit away from home and friends and nobody knew what I was doing at the time. I felt all alone. I thought of my girl friend by her name only. I relived the experience of walking through the first floor of the new City-County Building, which I had done two hours before the experiment began. I thought at that time: Is this real? Did I really do this, or did I dream that I went to the City-County Building? I remember clearly that I couldn't answer those questions."

In addition to the neutral content of the hypnagogic responses mentioned above, more intense experiences relevant to central conflict areas were evoked in patient subjects. In contrast to the predominantly visual-spatial reference of the neutral responses, affectivity was the outstanding feature of these abreactive responses.

A patient recalled a disturbing childhood event, involving a head injury to his twin brother, who had smashed his head against a steel bar. As the patient remembered his brother's bloody head, he experienced the various "weird and creepy" feelings associated with the event. Another patient tearfully abreacted his mother's death, a precipitating factor in his illness. These illustrations were taken from patient protocols. In general, normal subjects did not report experiences relevant to areas of deep personal conflict.

Feelings of Inebriation.—Occasional euphoria was seen. When it occurred, the subjects would often smile vacuously and compare their feelings to those resulting from several Martinis. "This is a cheap hang-over" and "I feel half-plastered" were characteristic responses. The majority of this group were normal subjects who were moderate social drinkers. In this connection, Griefenstein gave Sernyl as an anes-

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thetic to a patient who developed a full-blown delirium tremens. He later discovered that the man was a chronic alcoholic.¹¹

Repetitive Motor Behavior.—There were many reactions which appeared to function as facilitators of sensory feedback. Body movements of a rhythmic type were demonstrated by both normal subjects and patients. These included rocking, head-rolling, and, less frequently, grimacing. A normal subject reported in his retrospective account: "I kept shaking the bottles up and down because it felt good. Then I discovered that it also felt good to make my arms move in a figure eight." There was a definite tendency to focus on those stimuli which could still be appreciated. The same normal subject stated: "I started to rub my lips and my face. I could feel my fingers on my face, my lips rubbing each other, and my fingers rubbing each other. It felt pleasant to stroke my face and smack my lips against each other." It was almost as though the intact sensory modalities were overvalued, if not erotized. Perhaps the same general interpretation could be applied to the instances of repetitive, chanting speech observed in several subjects.

Neurological Changes

With the dose of 0.1 mg. per kilogram, the neurological changes were not as severe as those reported by Meyer et al.¹⁸ Diminution in pain, touch, and position sense occurred uniformly. All subjects displayed rotatory nystagmus and ataxic, slapping gait. Some subjects showed diplopia. There were a slight increase in muscle tone and minimal to mild impairment in motor strength. There was also a mild diminution in auditory and visual acuity. A centrally produced nausea occurred in several subjects.

Drug Effects on Schizophrenic Patients

Sernyl was given to four chronic schizophrenic subjects with illnesses of 8 to 10 years' duration, and one acute, mute, unresponsive catatonic patient. In the chroni-

cally ill patients, there was an intensification of the thought disorder, together with the stimulation of considerable affect. It was as though in these patients the acute phase of the illness had been reinstated. Sexual acting out, with professions of love toward personnel, was observed. One patient kept screaming: "I want to fuck; I love to eat; I love to fuck. Can I help it?" Another wanted to be kissed and fondled; however, the warmth and amiability were transient. The chronic patients generally became more assertive, hostile, and unmanageable. Withdrawal was less in evidence, and they tended to relate more to other patients and personnel, although in a meddlesome and aggressive manner. It was interesting that all four chronic patients manifested behavioral changes, which have continued for one month. The acute catatonic patient seemed completely unresponsive to the drug, his catatonics, if anything, being intensified. Four days later, he spontaneously emerged from his stuporous state and was able to recall his drug experience. He had been aware of the infusion and remembered feeling as though he were "returning to earth from another planet." His improvement was maintained for six weeks.

Comment

There is an impressive similarity between the psychopathology resulting from the intravenous administration of Sernyl and certain primary symptoms of the schizophrenic process. The disturbance in associations, inability to maintain a set, and concreteness produced by the drug were accompanied by none of the kaleidoscopic, visual, hallucinatory phenomena so characteristic of LSD-25 and mescaline.^{13,21} This would seem to distinguish Sernyl from these psychotomimetic agents, which might be said to mimic the secondary or restitutive symptoms of schizophrenia, while only minimally impairing the ability to associate, abstract, and maintain attention.^{4,10,22} The fact that the drug uniformly intensified the primary symptoms of a small group of schizophrenic patients also suggests that it

may act in a way fundamentally different from LSD or mescaline. Patients with chronic schizophrenia are highly resistant to the latter drugs and are able to discriminate between the drug effects and the usual manifestations of the psychosis.⁴ In contrast, Sernyl exaggerated their associational defect, and frequently their inappropriate affectivity. It also resulted in feelings which were more characteristic of the acute and earlier phases of the illness. In these patients, it is puzzling that behavioral changes persisted for weeks following Sernyl administration; this suggests that the action of the drug may touch upon some fundamental aspect of the disease.

Comparisons can be drawn between the effects of Sernyl and those changes occurring with environmental sensory isolation.¹⁶ In both experimental settings there is an attempt to diminish sensory input. With sensory isolation this effort is relatively successful with respect to exteroceptive stimuli, but inadequate with respect to proprioceptive stimuli. Prominence of personal reverie, impairment of directed thinking, and occasional disturbances in body image have been reported in these studies.^{2,18,20} With Sernyl the changes observed were similar, but far more intense, particularly with respect to distortions of body image and thinking.

The sequence in which symptoms became manifest following Sernyl infusion may be of particular importance. The first to appear was a disturbance in body image, with feelings of unreality, estrangement, and depersonalization. Then the disturbance in thinking emerged, characterized by inability to maintain a set, concreteness, blocking, and disordered linguistic expression. Following this, hostility and negativism were noted. Throughout the sequence, apathy became increasingly prominent.

The mechanisms by which Sernyl produces these changes are as yet obscure. It can be speculated that impaired transmission or central integration of proprioceptive feedback constitutes a necessary condition for the process observed. The nuclear im-

portance of the body image in psychological functioning has been repeatedly emphasized. Freud stated that "the ego is primarily a bodily thing, that is, the perception of one's own body. The body image is the nucleus of the ego."⁹ Schilder¹⁹ and Angyal¹ emphasized the significance of kinesthetic input and the postural model in neurosis and psychosis. Federn considered depersonalization to be the core of the schizophrenic process.⁸ In this connection he pointed out that "it could be clearly recognized that the bodily ego is formed by the proprioceptions transmitted through the sensorial nerves plus a uniting cathectic."⁸ Kubie has long emphasized the bipolar nature of the symbolic process with its anchor in the body image: "Thus the earliest learning builds on intrabodily experience, and the expanding knowledge of the external world relates itself automatically to those body impressions which have already been experienced internally."¹⁴

The experiments of Roger, Rossi, and Zirondoli present further evidence indicating the dependence of conscious states upon the maintenance of intact proprioception.¹⁷ These authors studied the effects of suppression of various afferent sources on EEG alertness patterns in *encéphale isolé* cats. EEG was maintained when olfactory, visual, acoustic, vestibular, or vagal sources were cut. EEG sleep rhythms resulted, however, from bilateral destruction of the Gasserian ganglion. Thus, a muscular origin of afferent feedback may be essential to the maintenance of normal states of wakefulness.

These considerations suggest that both the model psychosis induced by Sernyl and certain primary symptoms of schizophrenia may have their basis in a dysynchrony or defect in proprioceptive feedback. This tentative formulation is consonant with psychological hypotheses emphasizing the role of kinesthesia in thinking and affect.

This hypothesis is a tentative one, and it is understandable that other meaningful hypotheses regarding the action of Sernyl

and the pathophysiology of schizophrenia may be postulated. For example, the direct action of this drug on the cerebral cortex may be of crucial significance for the production of the thinking disturbance observed. Experiments to clarify the validity of these various hypotheses are being developed.

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Effects of Electroconvulsive Therapy on Blood Carbonic Anhydrase Activity in Man

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Convulsions induced electrically for the treatment of mental disease give rise to marked anoxia, hypercarbia, and acidosis.¹ These changes constitute a severe stress upon respiratory mechanisms of the blood, and it was therefore considered important to ascertain whether they might affect blood carbonic anhydrase activity.

Materials and Methods

Twelve patients, ranging in age from 38 to 67, were studied; nine were women. All had affective psychosis or schizophrenia. None had evidence of cardiovascular or respiratory disease, except for mild hypertension or emphysema in three. In two of the patients the violence of the convulsions was moderated by means of curare (solution of tubocurarine chloride U. S. P.). Studies were made before the first treatment and one to three days after subsequent treatments; in two instances additional measurements were made 10 and 19 days, respectively, after the last treatment. The method used is described elsewhere²; measurements were made of the activity of the enzyme in venous blood at 37°C (98.6°F).

Observations

The blood carbonic anhydrase activity before treatment ranged from 1.3 to 2.0 units per milliliter of whole blood and averaged 1.8 units per milliliter of whole blood (Table). The values for carbonic anhydrase activity per milliliter of erythrocytes were between 2.8 and 5.6 units; the average was 4.2 units. All but one of the values were under 5.0 units, the one exception (Case 7) being a patient with macrocytic anemia associated with liver disease.

In eight of the patients, all treated three times weekly, the blood carbonic anhydrase

activity rose during the course of treatment to between 1.6 and 3.1 units per milliliter of blood, or 3.5 and 6.7 units per milliliter of erythrocytes (Table). The averages were 2.4 and 5.5 units, respectively. The percentage increase in the activity per milliliter of erythrocytes in these patients was between 9 and 68 and averaged 42; in all cases but one the amount of change was greater than the spontaneous variation that might have occurred during the period of study. In two of these patients (Cases 2 and 4) the activities fell to normal 19 and 10 days, respectively, after the last treatment (Table). In two other patients (Cases 8 and 9) the activity fell when the schedule of treatment was changed to one every five days (Table). Measurements made in four cases sometime after the last treatment, or after the schedule of treatment had been changed to less than three a week, yielded values that differed from the control carbonic anhydrase activities by between +3% and -14%, with an average of -5%.

Four patients showed no rise in blood carbonic anhydrase activity while receiving electroshock therapy: One of these was a patient treated only once weekly; two patients (Cases 11 and 12), treated three times weekly but given curare to moderate the intensity of the seizures induced, also exhibited no increase in blood carbonic anhydrase activity. The fourth patient in this group was an alcoholic woman with liver disease and a macrocytic anemia.

Comment

Untreated patients with uncomplicated mental disease have normal blood carbonic anhydrase activity. Convulsions induced in

Submitted for publication June 27, 1958.

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ECT EFFECTS ON BLOOD CARBONIC ANHYDRASE

Blood Carbonic Anhydrase Values Following Electroconvulsions

Case	Sex	Age	Blood Carbonic Anhydrase			Comment
			Units per Ml. Blood	Units per Ml. Red Cells	Per Cent Change	
1	M	48	1.9	4.0	..	Before treatment
			3.1	6.5	+63	After 5th treatment (3 per week)
			2.9	6.6	+65	After 10th treatment (3 per week)
2	M	54	1.8	4.0	..	Before treatment
			2.9	6.7	+68	After 9th treatment (3 per week)
			1.6	3.7	-8	19 days after last treatment
3	F	61	1.7	3.8	..	Before treatment
			2.2	5.5	+45	After 9th treatment (3 per week)
4	F	58	1.9	4.2	..	Before treatment
			2.3	5.2	+24	After 9th treatment (3 per week)
			1.6	3.6	-14	10 days after last treatment
5	F	40	1.5	3.4	..	Before treatment
			1.6	3.7	+9	After 9th treatment (3 per week)
6	M	33	1.3	2.8	..	Before treatment
			1.6	3.5	+25	After 9th treatment (3 per week)
			1.7	3.5	+25	After 15th treatment (3 per week) Also received insulin daily
7	F	38	2.0	5.6	..	Before treatment
			1.8	4.9	-13	After 9th treatment (3 per week) Had cirrhosis of liver with macrocytic anemia
8	F	45	1.9	4.0	..	Before treatment
			2.9	6.6	+65	After 11th treatment (3 per week)
			1.8	4.1	+3	After 3 more treatments (every 5 days)
			1.7	3.7	-8	After 31st treatment (last 20 every 5 days)
9	F	58	1.9	4.5	..	Before treatment
			2.0	5.3	+18	After 6th treatment (3 per week)
			1.8	4.5	±0	After 7 more treatments (every 5 days)
10	F	46	2.0	4.3	..	Before treatment
			1.7	4.0	-7	After 4th treatment (1 per week)
11	F	67	2.1	4.0	..	Before treatment
			1.6	3.6	-10	After 9th treatment (3 per week); curarized
12	F	36	1.7	4.2	..	Before treatment
			1.5	3.7	-12	After 3d treatment (3 per week)
			1.6	3.9	-7	After 10th treatment (3 per week); curarized

such patients three times weekly and not moderated by curare caused a rise in blood carbonic anhydrase activity; this increase persisted for only a few weeks after the last treatment. The use of curare with the convulsions prevented a rise in blood carbonic anhydrase activity; similarly, the induction of seizures at intervals of only five or seven days did not result in an increase in the activity of carbonic anhydrase in the blood. Between treatments the patients were largely sedentary, or at most engaged in mild physical activity. The vio-

lence of the convulsions and their frequency appear to be important in determining whether or not increases in carbonic anhydrase activity will occur.

All patients in the present study showed partial to complete remission of their mental symptoms. It is clear from the observations here recorded that there is no necessary relation between increase in blood carbonic anhydrase activity and remission of mental disease; the latter occurred in the subjects in whom curare had been used and

persisted in patients in whom treatment was stopped or reduced in frequency.

Whether or not changes in brain tissue carbonic anhydrase activity parallel those which occur in the blood in patients given electroconvulsive therapy is not known. The question arises because Ashby^{3,4} considers loss of cerebral carbonic anhydrase activity to play an important role in the development of psychosis. However, the large errors which can occur during quantitative studies of tissue carbonic anhydrase require that the results of her studies be interpreted with caution. At any rate, no statement can be made with respect to the relevance of the present study to her hypothesis.

The mechanism of the change in blood carbonic anhydrase activity here described is not known. It is not clear whether there is an increase in enzyme concentration or merely in enzyme activity, the latter due to changed conditions in the blood. Nevertheless, the evidence indicates that frequently recurrent, severe respiratory acidosis gives rise to an increase in the activity of a blood enzyme involved in the transport of carbon dioxide.

Summary and Conclusions

Blood carbonic anhydrase activity increased in most patients in whom convulsions were induced for the treatment of mental disease. The violence and frequency of the seizures determined whether or not the increase occurred. It is concluded that these changes are not the cause of the therapeutic response to electroshock therapy. The possible importance of the findings in regard to the physiology of acidosis is discussed.

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Simple and Choice Reaction Times in Schizophrenia

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In a recent study of simple and choice reaction times in patients with cerebral disease, it was found that simple reaction time differentiated brain-damaged and control patients quite as well as did choice reaction time.¹ Indeed, in a number of comparisons, simple reaction time appeared to be a somewhat more effective discriminator than choice reaction time. These results led to the conclusion that a fundamental behavioral consequence of cerebral disease may be an impairment in the performance of simple, high-speed tasks. At the same time, the findings offered no support for any principle which would positively relate a differential degree of retardation to the complexity of the involved function.

These findings may be compared with the results of Huston and his associates on reflex time, simple reaction time, and choice reaction time in schizophrenic patients and normal subjects, which appeared to be in accord with such a principle.^{2,3} In these studies, no significant difference in patellar reflex time was found in the two groups. On the other hand, significant differences in both simple and choice visual reaction times were observed, the absolute size of the time difference being considerably larger in the case of the choice reaction.

This comparison raises the question as to whether schizophrenic and brain-damaged patients might not be differentiated from each other on the basis of the pattern of

Submitted for publication July 21, 1958.

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This investigation was supported by a research grant (B-616) from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, U. S. Public Health Service.

simple and choice reaction time responsiveness, the performances of schizophrenic patients being characterized by a more marked retardation in choice reaction time than in simple reaction time, and those of patients with cerebral disease being characterized either by the reverse pattern or by no differential retardation in the two types of reaction. To investigate this possibility, the reaction time study which had been done on patients with cerebral disease was replicated on a group of schizophrenic patients and the findings compared with those secured on the brain-damaged and control patients of the previous study.

Method

Subjects.—Sixty male schizophrenic patients at the Veterans Administration Hospital, Knoxville, Iowa, formed the experimental group. The mean age was 34.0 years, and the mean educational level was 10.4 years. The median time since first hospitalization was 3 years 8 months, the range being 4 months to 16 years 3 months.

The control group consisted of 30 patients on the neurological, neurosurgical, and medical services of the University Hospitals, Iowa City, who showed no evidence or history of cerebral disease, head injury, or epilepsy. Any patient who was acutely ill, who had a history of hospitalization for a psychiatric disorder, or whose history suggested mental defect dating back to childhood was excluded from consideration. A variety of diagnoses was represented in this group of patients, spinal cord disease being the most frequent (50%). Nine cases were classified as psychoneurotic with somatic complaints. The mean age was 38.5 years, and the mean educational level was 10.0 years. There were 18 men and 12 women in the group.

As estimated by *t*-tests, there was no significant difference between the two groups with respect to mean age or educational level.

Procedure.—The reaction time apparatus which was employed was identical with that used in previous studies.^{4,6,5} It provided for the presentation of a light stimulus, which was preceded by a buzz of two seconds' duration, the latter serving

as a warning signal. In the simple reaction task, the patient rested his right hand lightly on a microswitch and was instructed to press the switch as soon as a light appeared. The function of the buzz as a warning signal was explained to him. Thirty test trials, preceded by five practice trials, were given. In the choice reaction task, the patient rested the index fingers of his right and left hands on corresponding microswitches and was instructed to press the appropriate switch when the right or the left light appeared. As in the simple reaction task, the light was preceded by a warning signal of two seconds' duration. Here, 5 practice trials preceded 30 experimental trials, consisting of 15 stimulations on the right side and 15 stimulations on the left side, presented in a predetermined random order.

In half of the schizophrenic group and in the total control group, the simple reaction task was given first and was followed, after a rest period of two to three minutes, by the choice reaction task. The other half of the schizophrenic group was given the tasks in reverse order. Since analysis disclosed no significant effects of order on simple and choice reaction times in the schizophrenic patients, these two subgroups were combined into a single group of 60 schizophrenic patients in the main treatment of results.

The reaction times were recorded in 0.01-sec. units by an electrically driven clock, which was activated by the onset of the light stimulus and was stopped by the depression of the appropriate microswitch. These times were separately summed and averaged to the nearest 0.001 sec. for each patient. An intraindividual variability measure (S. D.) was also computed on the basis of the time-score data. Because some of the distributions of the mean scores were skewed (Fig. 1), these time scores were transformed to speed scores by taking the reciprocal of each patient's mean time score in 0.01-sec. units and multiplying it by 1,000. This transformation resulted in distributions of speed scores which were essentially normal, and which were thus more appropriate for certain statistical analyses.

Results

The mean simple reaction time for the control patients was 0.208 sec. (S. D. 0.040 sec.) and that for the schizophrenic patients was 0.265 sec. (S. D. 0.052 sec.). This difference in means was found to be highly significant ($P < 0.001$), as estimated by a nonparametric *t*-test (Cochran-Cox). Taking the performance of the control group as a criterion, the schizophrenic patients showed a retardation of approximately

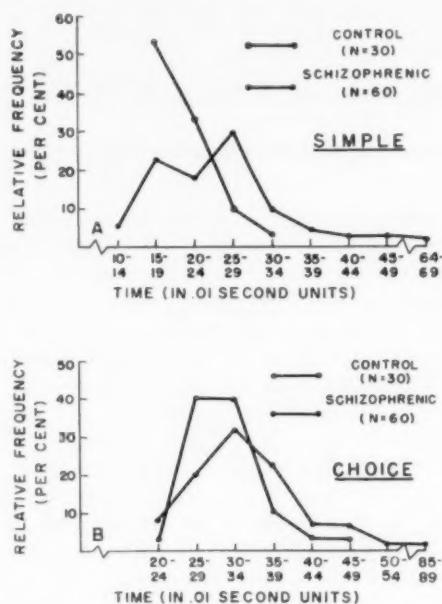


Fig. 1.—Distribution of reaction times in schizophrenic and control patients.

27% in simple reaction time. Fourteen schizophrenic patients (23%) showed simple reaction times which were slower than the simple reaction time of the slowest control subject (Fig. 1).

The mean choice reaction time for the control patients was 0.310 sec. (S. D. 0.046), while that for the schizophrenics was 0.350 sec. (S. D. 0.093). The difference in mean scores was found to be significant ($P < 0.05$), as estimated by a nonparametric *t*-test (Cochran-Cox). Taking the performance of the control group as a criterion, the schizophrenic patients showed a retardation of 13% in choice reaction time. Five schizophrenic patients (8%) showed choice reaction times which were slower than that of the slowest control patient.

The mean speed scores of the two groups of patients for simple and choice reactions are shown in Figure 2. It will be noted that the patterns of the two groups appear to differ in the direction of a smaller separation between the groups at the choice-

SIMPLE AND CHOICE REACTION TIMES

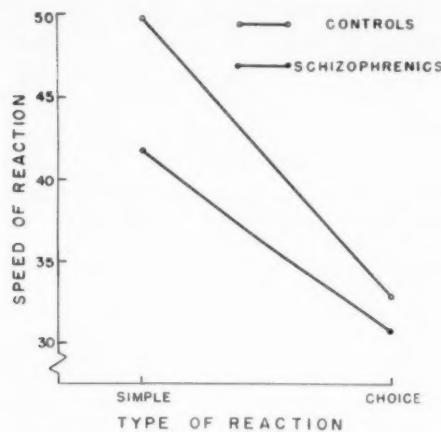


Fig. 2.—Mean speed scores of schizophrenic and control patients.

reaction point. This impression was confirmed by the results of a Type I analysis of variance applied to these speed scores, which indicated significant main effects for diagnostic category and type of reaction and also a significant interaction between the two factors. The schizophrenic patients were significantly slower ($P < 0.005$) than the controls ($F = 9.10$; $d. f. 1, 88$), and speed of choice reaction was significantly slower ($P < 0.001$) than speed of simple reaction ($F = 218.09$; $d. f. 1, 88$). Moreover, there was a greater difference between control and schizophrenic patients in speed of simple reaction than in speed of choice reaction ($F = 7.11$; $d. f. = 1, 88$; $P < 0.01$).

Interindividual Variability.—When the variances of the distributions of simple and choice speed scores in the two groups were compared, it was found that those of the schizophrenic patients were significantly more variable in both performances. Simple analysis of variance of the speed scores yielded an F of 2.01 ($d. f. 59, 29$; $P < 0.025$) for the simple reaction and an F of 2.03 ($d. f. 59, 29$; $P < 0.025$) for the choice reaction.

Intraindividual Variability.—The mean intraindividual standard deviation in simple reaction time was found to be 0.043 in the

control patients and 0.074 in the schizophrenic patients. This difference in mean variability was found to be significant ($P < 0.001$) on the basis of an analysis of the mean intraindividual variances of the two groups ($F = 2.88$; $d. f. 59, 29$). On the other hand, the difference in the mean intraindividual standard deviations for choice reaction time (0.062 in the control patients and 0.074 in the schizophrenic patients) was found to be nonsignificant ($F = 1.41$; $d. f. 59, 29$).

Comparison with Brain-Damaged Patients.—The brain-damaged patients investigated in our previous study were somewhat slower in reaction time than the schizophrenic patients in the present study, their mean simple reaction time being 0.303 sec. and their mean choice reaction time being 0.386 sec.¹ However, as compared with the control patients, the performance patterns of the brain-damaged and schizophrenic groups were the same; i. e., both showed a greater absolute and relative retardation in simple than in choice reaction time. In addition, both the brain-damaged and the schizophrenic patients showed greater interindividual and intraindividual variability than the control patients.

Comment

The findings show that schizophrenic patients exhibit a more marked retardation in simple reaction time than in choice reaction time when the performances of control patients are taken as a standard. These results are quite comparable to those previously obtained on patients with cerebral disease, and they indicate that schizophrenic and brain-damaged patients show the same pattern of performance with respect to simple and choice reaction times.

No ready explanation of the discrepancy between the present findings and those of the earlier study of Huston³ can be offered. However, the results of both studies are in agreement in their indications of a greater relative retardation in simple than in choice reaction time in schizophrenics. Moreover, the results of the recent investigation by

King⁶ of reaction time to sound in schizophrenic patients and normal subjects, while not altogether comparable because of certain features of his procedure, are in accord with those of both studies in this regard.

In summary, impairment in the performance of simple, high-speed tasks appears to be a salient behavioral feature in many cases of cerebral disease and schizophrenia. It is possible to interpret this finding in a variety of ways. It might be concluded that those schizophrenic patients who show marked retardation in simple reaction time constitute a special "brain-damaged" subgroup of the diagnostic category. Or it might be concluded that, while the underlying pathologic processes are quite different in the two categories, a common end-result is a motivational or other type of deficit which leads to a basic retardation in responsiveness. Since evaluation of the tenability of these or other hypotheses would require

consideration of a wide range of data, it is beyond the scope of this experimental report.

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Medical Student Orientations Toward the Emotionally Ill

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The doctor-patient relationship has long been recognized as a vital aspect of the healing arts. In this relationship the doctor deals with the essentially human dimensions of illness which are manifested in his patient's personal feelings and attitudes about his disease, about the environment in which he plays a sick role, and about the doctor himself. No less important than the patient's attitudes, however, are the feelings, thoughts, and modes of relating to others which the doctor brings to the relationship, for these may significantly facilitate or limit his effectiveness in treating patients.

Doctors often encounter difficulty in treating and relating to patients who make them feel anxious. The problem of defending against patient-induced anxiety is especially acute for the medical student, because his experience and competence are necessarily limited. In the course of learning to handle his anxieties the student may be expected to acquire general attitudes of a defensive nature toward those types of patients he finds especially threatening. Because emotionally ill patients appear to provide an abundant source of threat, the present study was designed to investigate the defensive aspects of senior medical students' orientations toward the emotionally ill.

Method

From a class of 30 students 22 volunteered as Ss for this study. Using Q-technique,² Ss described their conceptions of three types of patients: an ideal patient, a typical organically ill patient, and a typical emotionally ill patient presenting complaints similar to those of the organically ill patient. The sorting of statements was in all cases

ordered into the specified eleven-point distribution: 1, 3, 5, 7, 10, 11, 10, 7, 5, 3, and 1, with the continuum running from least characteristic to most characteristic. Scores from 1 to 11 were assigned to the eleven intervals and consequently to the statements which Ss assigned to each interval. The item population consisted of 63 statements designed to sample a wide range of relevant attitudes displayed by patients, such as skepticism and confidence in the doctor, excessive worry and denial regarding illness, resistiveness and cooperativeness in regard to treatment, secondary gain, etc. In general, 21 of these statements referred to the doctor, 21 referred to treatment, and 21 to illness.

An average description of each of the three types of patients was obtained by summing the scores for each statement on each sort across the 22 Ss. The 22 descriptions of the typical emotionally ill patient were then intercorrelated, and the resulting matrix was factored by the centroid method. Four orthogonal factors were obtained and rotated to an oblique simple structure solution.

In order to derive a composite sort for each factor extracted from the emotionally ill patient correlation matrix, only Ss relatively pure on one factor were used.* The weights for each pure S were obtained by the formula $\frac{r_{pt}}{(1-r_{pt}^2)}$, where r_{pt} represents a S's factor loading on the factor to be defined. Though this formula was originally suggested by Spearman³ as a best estimate for use with orthogonal factors, its applicability to the present procedure utilizing oblique factors was clearly justified by the agreement of the correlations among the four derived composite sorts and the original correlations among the factors obtained directly from the cosine matrix. The mean difference among the six comparable pairs of correlations was 0.08.

* In an attempt to equalize the distribution of variance among the three remaining factors, several apparently pure Ss were eliminated from determining the third factor. The composite sorts for the four factors were based on 3, 3, 4, and 2 Ss, respectively.

Submitted for publication May 28, 1958.

Department of Psychiatry, University of California at Los Angeles School of Medicine.

Results

The eight highest and eight lowest statements for the average description of each of the three types of patients are listed below. Together, they provide a frame of reference for consideration of the factors derived from the emotionally ill patient sorts.

Average Description of the Ideal Patient

Most Characteristic Statements

Statement

No.

- 48 Accepts appropriate responsibility for carrying out his treatment
- 40 Able to assess realistically his symptoms, their import, and their treatment
- 30 Can understand and accept the fact that his physician may not always know exactly what's wrong with him
- 17 Would find satisfaction in knowing that everything possible was done for him, even if his symptoms were not completely removed
- 29 Would be satisfied with a reasonable therapeutic outcome
- 63 Remains calm and sensible in thinking about his illness
- 56 A reasonably good result can be expected in his case
- 44 Willing to try any treatment program his physician recommends

Least Characteristic Statements

- 26 Obtains inward satisfaction from seeing his physician's treatment fail
- 18 May not wholeheartedly want to get well
- 59 Resists care he realistically should have
- 52 Quick to want to try unproved, or even quack remedies he has heard about
- 10 May deliberately hide certain aspects of his illness and stress others
- 62 Inclined to feel that his physician doesn't understand his case and is experimenting on him
- 16 May forget or be careless in following his physician's treatment recommendations
- 60 Apt to present vague, unspecific, and changeable complaints

Average Description of the Organically Ill Patient

Most Characteristic Statements

Statement

No.

- 9 Feels better just knowing that his physician is doing something for him
- 44 Willing to try any treatment program his physician recommends

- 55 Grateful to his physician for any relief he obtains through treatment
- 12 Wants much reassurance from his physician that his illness is not serious
- 36 If one treatment program doesn't work, he is ready to try another approach
- 49 Believes that ultimately his physician will find ways to treat him successfully
- 15 Motivated to have his physician regard him as a good patient
- 53 Concerned about the effects of his illness on his family and loved ones

Least Characteristic Statements

- 26 Obtains inward satisfaction from seeing his physician's treatment fail
- 22 Inclined to be somewhat cynical and hesitant about his physician's recommendations
- 59 Resists care that he realistically should have
- 39 Inclined to be passive about doing anything for himself that will aid the treatment
- 62 Inclined to feel that his physician doesn't understand his case and is experimenting on him
- 35 Acts as if he blames his illness on others
- 45 Will only countenance a physician who relates to him on his own terms, even though this may exclude aspects of his case the doctor feels are important
- 19 Inclined to blame himself for any setbacks or slow progress in treatment

Average Description of the Emotionally Ill Patient

Most Characteristic Statements

Statement

No.

- 60 Apt to present vague, unspecific, and changeable complaints
- 5 Tends to overdramatize and exaggerate his symptoms
- 1 Feels that an ill person deserves care and sympathy from others
- 7 Generally apt to let others know that he is ill or under medical care
- 13 Makes more demands on others because of his illness
- 28 Inclined to use his symptoms to lighten or avoid his adult responsibilities
- 18 May not wholeheartedly want to get well
- 43 Feels that his illness permits him to obtain considerations or concessions he ordinarily could not expect

Least Characteristic Statements

- 14 Seeks to give others the impression he has no symptoms at all
- 37 Stoic about his suffering

MEDICAL STUDENT ORIENTATIONS

TABLE 1.—Original and Rotated Factor Matrices from Emotionally Ill Patient Sorts

Sorter	Original Factors					Rotated Factors			
	I	II	III	IV	b^2	A	B	C	D
1	0.59	0.18	-0.26	-0.23	0.50	0.43	0.11	0.05	-0.07
2	0.55	0.36	-0.29	-0.04	0.52	0.39	0.01	-0.07	0.15
3	0.41	0.14	-0.19	-0.05	0.23	0.27	0.01	0.05	0.04
4	0.63	0.11	0.19	-0.21	0.49	0.02	0.42	0.14	0.08
5	0.69	0.17	0.07	-0.20	0.55	0.12	0.35	0.11	0.09
6	0.70	0.14	0.12	-0.16	0.55	0.08	0.36	0.15	0.12
7	0.57	-0.46	-0.02	0.10	0.55	0.07	-0.07	0.08	-0.05
8	0.09	-0.38	0.24	0.08	0.68	-0.14	0.17	0.66	0.09
9	0.74	-0.38	-0.04	-0.04	0.69	0.17	0.05	0.65	-0.09
10	0.82	-0.30	0.23	0.05	0.82	-0.09	0.23	0.61	0.12
11	0.75	-0.29	-0.06	-0.01	0.65	0.18	0.14	0.58	-0.03
12	0.82	-0.21	-0.01	-0.04	0.72	0.16	0.13	0.54	0.01
13	0.85	-0.14	0.02	0.06	0.75	0.11	0.11	0.52	0.14
14	0.58	0.32	-0.14	0.36	0.59	0.12	-0.13	0.08	0.50
15	0.71	0.31	0.01	0.11	0.61	0.09	0.15	0.08	0.38
16	0.82	-0.10	-0.16	-0.06	0.71	0.31	0.06	0.44	0.00
17	0.73	-0.23	-0.26	-0.09	0.66	0.39	-0.04	0.50	-0.14
18	0.56	0.39	0.19	0.02	0.50	-0.06	0.33	-0.08	0.38
19	0.78	0.06	-0.01	0.15	0.63	0.10	0.07	0.34	0.29
20	0.81	0.10	0.03	0.27	0.74	0.03	0.04	0.35	0.42
21	0.70	0.17	0.09	0.05	0.53	0.03	0.21	0.18	0.29
22	0.71	0.05	0.11	-0.06	0.52	0.05	0.20	0.26	0.15

- 40 Able to assess realistically his symptoms, their import, and their treatment
- 2 Endeavors to let his symptoms interfere with his life as little as possible
- 63 Remains calm and sensible in thinking about his illness
- 61 Tries to find some humor or lightness in his situation
- 57 Would like to be told that there is nothing really wrong with him, that he needs a rest or vacation
- 33 Comforted by the fact that he is not as ill as many patients

The original centroids and rotated factors from the emotionally ill patient sorts are presented in Table 1.[†] Henceforth the four rotated factors will be referred to as orientations toward the emotionally ill. The correlations among the orientations are given in Table 2. The eight highest and eight lowest statements for each orientation, together with a vignette of each, are given below.

Orientation A

Most Characteristic Statements

- | | |
|-----------------------------------------------------------------|-----|
| Statement | No. |
| | 1 |
| Feels that an ill person deserves care and sympathy from others | |

[†] A complete list of the Q-statements, the correlation and transformation matrices, are available from us on request.

TABLE 2.—Correlations Between Primary Factors

	A	B	C	D
A	1.00			
B	0.62	1.00		
C	0.36	0.42	1.00	
D	0.68	0.47	0.35	1.00

- 7 Generally apt to let others know that he is ill or under medical care
- 60 Apt to present vague, unspecific, and changeable complaints
- 36 If one treatment program doesn't work, he is ready to try another approach
- 13 Makes more demands on others because of his illness
- 18 May not wholeheartedly want to get well
- 10 May deliberately hide certain aspects of his illness and stress others
- 30 Can understand and accept the fact that his physician may not always know exactly what's wrong with him
- Least Characteristic Statements
- 14 Seeks to give others the impression he has no symptoms at all
- 19 Inclined to blame himself for any setbacks or slow progress in treatment
- 61 Tries to find some humor or lightness in his situation
- 51 Readily critical of his physician, even though he doesn't express this directly
- 33 Comforted by the fact that he is not as ill as many patients

- 40 Able to assess realistically his symptoms, their import, and their treatment
- 46 Takes any temporary relief he gets from treatment to mean that there is now nothing wrong with him
- 37 Stoic about his suffering

Ss of Orientation A view the emotionally ill patient as hiding some aspects of his illness from his physician and as not really wanting to get well. He is described as compliant, uncritical, and unblaming in regard to both his treatment and his doctor, as presenting vague complaints, as utilizing secondary gain, and as making few, if any, inappropriate demands for medical help. In short, he appears essentially uninvolved with his physician, either positively, in terms of motivation to get well, or negatively, in terms of demands or hostility.

Orientation B

Most Characteristic Statements

Statement

- No. 7 Generally apt to let others know that he is ill or under medical care
- 1 Feels that an ill person deserves care and sympathy from others
- 13 Makes more demands on others because of his illness
- 36 If one treatment program doesn't work, he is ready to try another approach
- 28 Inclined to use his symptoms to lighten or avoid his adult responsibilities
- 23 Highly desirous of keeping his physician's friendship and respect
- 43 Feels that his illness permits him to obtain considerations or concessions he ordinarily could not expect
- 44 Willing to try any treatment program his physician recommends

Least Characteristic Statements

- 14 Seeks to give others the impression he has no symptoms at all
- 37 Stoic about his suffering
- 40 Able to assess realistically his symptoms, their import, and their treatment
- 30 Can understand and accept the fact that his physician may not always know exactly what's wrong with him
- 33 Comforted by the fact that he is not as ill as many patients
- 57 Would like to be told that there is nothing really wrong with him, that he needs a rest or a vacation
- 2 Endeavors to let his symptoms interfere with his life as little as possible

- 63 Remains calm and sensible in thinking about his illness

Ss of Orientation B characterized the emotionally ill patient as primarily exploiting his symptoms for secondary gain and thus wallowing in his illness. He is seen as a passive, compliant person who idealizes his doctor and who, by being an obedient patient, seeks to insure his claim to the sick role. Compensation through secondary gain is central in this orientation.

Orientation C

Most Characteristic Statements

Statement

- No. 60 Apt to present vague, unspecific, and changeable complaints
- 5 Tends to overdramatize and exaggerate his symptoms
- 6 Compares his physician with others he has heard about; tends to shop around for a doctor he likes
- 7 Generally apt to let others know that he is ill or under medical care
- 13 Makes more demands on others because of his illness
- 1 Feels that an ill person deserves care and sympathy from others
- 51 Readily critical of his physician, even though he doesn't express this directly
- 28 Inclined to use his symptoms to lighten or avoid his adult responsibilities

Least Characteristic Statements

- 37 Stoic about his suffering
- 61 Tries to find some humor or lightness in his situation
- 14 Seeks to give others the impression he has no symptoms at all
- 63 Remains calm and sensible in thinking about his illness
- 11 Puts his case in his physician's hands and trusts him completely
- 32 Optimistic about the outcome of treatment
- 56 A reasonably good result can be expected in his case
- 21 Despite any fears he has, he wants to know what's really wrong with him

Ss manifesting this orientation describe the emotionally ill patient as critical and untrusting of his doctor. They view him as making exaggerated demands on others and as being pessimistic about the possibilities of getting what he wants. In brief, he is characterized by aggressive demands for what he feels is his due.

MEDICAL STUDENT ORIENTATIONS

Orientation D

Most Characteristic Statements

- Statement No.
- 31 Overemotional and excessively worried about any possibly serious aspects of his illness
 - 60 Apt to present vague, unspecific, and changeable complaints
 - 9 Feels better just knowing that his physician is doing something for him
 - 3 Presents information about his personal life and feelings, his reactions to his symptoms, and his fears and anxieties of various sorts
 - 15 Motivated to have his physician regard him as a good patient
 - 55 Grateful to his physician for any relief he obtains through treatment
 - 12 Wants much reassurance from his physician that his illness is not serious
 - 20 Inclined to cling to his physician, even though told that nothing more can be done for him

Least Characteristic Statements

- 4 May be skeptical about the ability of a young physician
- 19 Inclined to blame himself for any setbacks or slow progress in treatment
- 40 Able to assess realistically his symptoms, their import, and their treatment
- 14 Seeks to give others the impression he has no symptoms at all
- 21 Despite any fears he has, he wants to know what's really wrong with him
- 46 Takes any temporary relief he gets from treatment to mean that there is now nothing wrong with him
- 59 Resists care that he realistically should have
- 33 Comforted by the fact that he is not as ill as many patients

Ss of this orientation view the emotionally ill patient almost exclusively in terms of his dependence on his doctor. They view him as a trusting, clinging, anxious person who seeks reassurance and support from his physician. In their eyes he resembles a clinging, frightened child.

Comment

Ss show marked agreement in their descriptions of the ideal patient. The mean correlation among Ss was 0.68, with a standard deviation of 0.07 for an N of 231. The average sort indicates that they view the

ideal patient as entirely sensible, as making minimal demands on his physician, and as calmly accepting whatever results his treatment produces. In short, he presents no personal feelings or attitudes which might in any way threaten his physician or complicate treatment. As he seems to share the doctor's perspective toward his illness, he is unlikely to be critical if treatment proves unsuccessful. Thus the ideal patient is, to the near exclusion of all else, a nonthreatening patient.‡

Ss' descriptions of the organically ill patient were somewhat similar to their descriptions of the ideal patient; the mean correlation between the two sorts was 0.41, for an N of 22. The organically ill patient is depicted as more dependent on his physician and more concerned over his illness than the ideal patient, but his treatment attitude and feelings toward his doctor are nevertheless positive. Because he does not display the ideal patient's complete objectivity toward his illness, the organically ill patient appears to be truer to life. However, like the ideal patient, he is essentially non-threatening to his doctor.

The average description of the emotionally ill patient illustrates the agreement among all Ss which is reflected in the factor intercorrelations of Table 2. His ambiguous complaints are apt to make diagnosis uncertain; his exaggerated demands on others are apt to make him difficult to satisfy, and his resistance to getting well is apt to nullify treatment. It thus appears that the emotionally ill patient is collectively characterized by attitudes which tend to hinder treatment and to threaten his physician.

Turning now to the factors derived from the descriptions of the emotionally ill patient, four distinct orientations emerged. These orientations indicate the varying attitudes, values, and expectations which doctors bring to such patients. Orientation C

‡ That such an ideal of objectivity, compliance, and acceptance would be considered pathological in other contexts is an interesting commentary on the meaning of the doctor-patient relationship to the student physician.

is most distinct and has the greatest number of high loadings. Though none of the orientations correlate well with grade-point averages, Ss of Orientation C are solid, capable medical students who represent, as one nonpsychiatric faculty member put it, a group of the best and the most conventional students. In content, this orientation appears least favorably disposed toward the emotionally ill patient. Using the ideal-patient sorts as a base line from which to measure the acceptability of the emotionally ill patient yields results which are consistent with this interpretation. This is seen in Table 3, which contains the correlations between each of the four orientations and the

"recognition" of the patient's resistances and lack of concern to avoid taking him too seriously or becoming threatened by him. Possible threats to their status or competence in the face of such recalcitrance may be compensated for by feelings of astuteness attending their awareness of the patient's covert motivations. They can dismiss such patients, attempt to treat them, or study them objectively, all with relative security. Because of the implication of intellectual mastery here, it is noteworthy that of the three Ss representing Orientation A, two intend to pursue research careers and the third has chosen psychiatry as a specialty.

Ss of Orientation B are most alert to the emotionally ill patient's use of his symptoms or his illness to receive from others. Indeed, they seem to lose sight of all else. As seen in Table 3, Orientation B is also relatively unfavorably disposed toward the emotionally ill patient. Although viewed as idealizing the doctor, the demands and expectations imputed to such patients are perceived as excessive. By focusing on secondary gain, guilt-free rejection is facilitated—"They've never had it so good."

In Orientation D the emotionally ill patient is viewed as compliant, trusting, and, above all, seeking extensive personal support from his physician. Several possible explanations might account for this monothematic characterization: (1) Dependence is the most threatening aspect of emotionally ill patients; (2) dependence is the aspect of emotionally ill patients, most comfortably handled, or (3) the emphasis on dependence represents a denial of more threatening aspects of emotionally ill patients, such as negative feelings toward the doctor. The lack of a high negative correlation between Orientation D and the average ideal patient sort (Table 3) helps to discount the first possibility. The latter two possibilities are not mutually exclusive and together might account for such an overdetermined view better than either individually. Judging from the average description of the ideal patient, the emotionally ill patient described in Orientation D is not an especially desirable pa-

TABLE 3.—Correlations Between the Four Orientations and the Average Ideal Patient Sort

Orientation	r	N
A	-0.03	63
B	-0.30	63
C	-0.71	63
D	-0.08	63

average ideal sort. The correlation between the array for Orientation C and the average ideal array was -0.71. We would further expect an inverse relationship between a Ss' loading on Factor C and the similarity between his conceptualizations of the ideal and the emotionally ill patients. Treating the 22 Ss' correlations between their ideal and emotionally ill patient sorts as scores and correlating these scores with their loadings on Factor C yielded a correlation of -0.86. The aggressiveness which Ss of Orientation C impute to the emotionally ill could reflect a projective mechanism or a heightened sensitivity to aggressiveness not shared by all Ss. In any case, the probable result would be avoidance and rejection of such patients.

Ss of Orientation A view the emotionally ill patient as resistive to getting well and hiding some aspects of his illness from his doctor. Being minimally involved in his treatment, he is neither negative toward nor demanding of his physician. This view suggests that Ss of this orientation use their

tient; yet this orientation does appear to afford the doctor some measure of security. It provides the basis for a working relationship which is relatively free from threats to the doctor's status and competence. By assuming a parental attitude toward the dependency needs imputed to emotionally ill patients, their potentialities for threatening the doctor are mastered. Such doctors may be inclined to treat the emotionally ill by assuming considerable direction and control over them and/or giving them extensive personal support. It is not inconceivable that this orientation could be related to the doctor's own symbiotic needs.

Of the four orientations, C is farthest removed from an understanding, accepting, and relaxed attitude toward the emotionally ill patient. We would not expect practitioners so oriented to evidence an inclination or an aptitude for psychotherapeutic work. The identification of this orientation and its relatively great popularity in the present group of Ss are perhaps the major findings presented here. In accordance with the above interpretations, psychiatrists might be expected to emerge from Orientations A and D. Only two Ss in the present population planned to specialize in psychiatry. One of these, as mentioned earlier, represents Orientation A, and the other, although a somewhat "mixed" type, ranks second highest on Orientation D.

Summary

Using Q-technique, 22 senior medical students described their conceptualizations of three types of patients: (1) an ideal patient, (2) a typical organically ill patient, and (3)

a typical emotionally ill patient presenting complaints similar to the organically ill patient. The Q-statements referred to patients' attitudes toward their illness, their treatment, and their doctor. Intercorrelating and factoring their descriptions yielded four orientations toward the emotionally ill. The average descriptions of the ideal patient and the organically ill patient provided a frame of reference for interpreting their images of the emotionally ill. The four orientations characterized the emotionally ill as follows:

- A. Resistive to getting well, passive in accepting treatment, and essentially undemanding toward his doctor
- B. Utilizing his illness to obtain secondary gain, and seeking to maintain the legitimacy of his claim to the sick role
- C. Aggressively demanding of all; critical and untrusting of his doctor
- D. Outstandingly compliant, dependent, and trusting toward his doctor

The implications each of the four orientations hold for the handling of patient-induced anxiety and for working with emotionally ill patients are discussed. In general terms, the differences in orientation indicate the diverse attitudes, values, and expectations which physicians may bring to the doctor-patient relationship.

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A Comparison of Chlorpromazine and EST in Treatment of Acute Schizophrenic and Manic Reactions

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Six years have elapsed since chlorpromazine had its first clinical trials. During that time over 1,200 separate reports on this drug have been published. Most of these reports have indicated clinical impressions of its value in all types of mental illness—chronic and acute. Most of the reports are laudatory.^{1-3,8-11,13-15}

At this time there seems to be general agreement that chlorpromazine and related compounds are useful in the treatment of psychiatric disorders. Now that the early wave of enthusiasm for the "psychiatric wonder drugs" has passed, we believe that it is necessary to compare the results of chlorpromazine treatment with those of other standard treatment methods. Only by evaluation under carefully controlled conditions can one come to any statistically defensible conclusions about its usefulness.

Electroshock therapy (EST) has been an accepted treatment method for acute schizo-

Submitted for publication July 23, 1958.

Thorazine was furnished for the study by Smith, Kline, & French Laboratories.

The Langley Porter Neuropsychiatric Institute, San Francisco, and Agnews State Hospital, Agnew, Calif. (Dr. Langsley). Agnews State Hospital: Presently: Director of Clinical Services, Porterville State Hospital, Porterville, Calif. (Dr. Enterline). Agnews State Hospital (Dr. Hickerson).

Dr. L. E. Moses, of the Department of Statistics, Stanford University, assisted in the experimental design and the statistical analysis of the results. Drs. Dean Archer, Fred Baer, Ames Fischer, Bernard Hansen, Raymond Leer, Stanley Milstone, Harold Nolen, and Fred Tempey assisted in rating and evaluating the results of treatment. The following ward personnel assisted in the rating of patients: Mrs. E. Ellis, R.N.; Mrs. M. Gran, R.N., and Mrs. H. Wachal, R.N.; and Mrs. H. Caldwell, Mrs. M. Ecklund, Mrs. C. Jodoin, Mrs. J. Price, and Miss C. Plinski, psychiatric technicians.

phrenic and manic reactions for a number of years. In this study we have attempted to compare under controlled conditions the effects of chlorpromazine (CPZ) and EST in these types of illnesses.

Methods and Procedures

Case Material.—The female acute treatment service of Agnews State Hospital provided adequate numbers of subjects for study. The criteria for selection of a patient for the study were as follows:

1. A clinical diagnosis of acute schizophrenic or manic reaction must have been established.
2. Symptoms of present psychotic episode must have been noted for less than three months.
3. If there was a history of a previous psychotic episode, the patient must have been in clinical remission for at least six months prior to the onset of the present illness.
4. The patients ranged in age from 18 to 45 years. Older patients were rejected to avoid including the involutional psychotic reactions in this study.

Selection of suitable cases was made by the two ward psychiatrists (D. G. L. and J. D. E.), who also were responsible for administering the treatment. The experimental design was planned in advance with the biostatistical consultant, Dr. L. E. Moses, and the psychologist for the project (G. X. H.). The two ward psychiatrists who selected patients for the project and administered treatment did not know at the time of selection what treatment the patient would receive and did not participate in the rating of patients or in the evaluation of the results of treatment. After a patient had been selected for the project by one of the two ward psychiatrists, the psychologist was notified, and he arranged for the initial psychiatric and ward ratings. When the initial ratings were completed, he notified the ward physicians of the treatment to be used according to a previously made random selection method.

Treatment Methods.—The EST patients received a course of electrically induced grand mal seizures over a period of eight weeks. The usual number of treatments ranged from 15 to 20, given three

CHLORPROMAZINE AND EST—COMPARISON

times weekly initially and gradually reduced in frequency to one per week. No chemical modification was used with the electroshock therapy.

The CPZ patients received a course of the drug (Thorazine) for eight weeks. In most cases drug administration was started parenterally and then changed to oral after two or three days. The average daily dose of chlorpromazine was approximately 800 mg., the range being 200 to 2,000 mg. Medication was usually given in four divided doses. In the last weeks of the treatment course, the dose was reduced gradually. Where maintenance chlorpromazine was indicated, it was given in the range of 100-200 mg. daily, in four divided oral doses. Patients who received the drug had base line and weekly white blood cell counts and urine examinations for bile.

All patients in the study were started on treatment on the same ward (the female acute treatment ward) and, when considered sufficiently improved by the ward psychiatrist, were transferred to one of two other treatment wards. The choice of the treatment ward was also made in advance by random selection and was controlled by the psychologist. Both the treatment wards were under the supervision of the two ward psychiatrists who administered the treatment. All patients in the study received the usual ward milieu treatment, hydrotherapy when indicated, and industrial therapy, and were included in occupational and recreational therapy and ward group psychotherapy along with other patients on the ward not in the study. Every effort was made to make the treatment program similar for all patients in the study so that the only variable would be that one group received EST and the other group received chlorpromazine.

Evaluation of Treatment.—There is no need to dwell on the difficulties of evaluating treatment methods in psychiatric illness. Much of the evaluation of chlorpromazine to date has consisted of clinical impressions. A number of scales have been devised in an effort to obtain numerical measurements of the degree of illness.^{4,5} No one method of evaluating the amount or degree of illness has been completely satisfactory. For purposes of this study, we believe that the efficacy of the treatment method can be measured in terms of (1) changes in ward behavior and adjustment as judged by the ward personnel, who spend more time observing patients than any other group; (2) clinical changes in the patient as measured by psychiatric interviewers, who rate patients on a scale for measuring degrees of psychotic illness; (3) clinical impressions of the ward psychiatrists responsible for the treatment of the patients, and (4) final evaluation of the efficacy of treatment, depending on whether it helps the patient become well enough to leave the hospital, how soon after

treatment begins she can leave the hospital, and how long she can remain out of the hospital. We have used the following measurement methods.

1. Evaluation by Ward Personnel: The Agnews revision of the Fergus Falls Behavior Rating Sheet¹⁸ was completed by the ward charge for each patient included in the study. This was done weekly for the first month of treatment, twice monthly for the second month, and monthly thereafter. The psychologist distributed the rating sheets to the wards and collected them, and neither the ward psychiatrists or other psychiatric raters had any knowledge of the ratings assigned by the ward personnel.

2. Evaluation by Psychiatrists: Each patient was interviewed individually by three psychiatrists on three different occasions: (a) at the time of selection for the study and before treatment was begun, (b) at the end of 8 weeks of treatment, and (c) 12 weeks after treatment was begun. Each psychiatrist saw the patient for a 15-minute interview and then completed the Hickerson-Goodrich Scale.^{6,7} The same raters saw the same patients on all three occasions. None of the raters were concerned with selection of patients for the study, assignment of treatment methods, or administration of the ward on which the patients were treated. After approximately half of the group had been rated by three psychiatrists on three separate occasions, the results of the ratings were subjected to statistical analysis for interrater agreement (*vide infra*). The degree of interrater agreement was considered sufficiently high that the last half of the group were rated by only one psychiatrist on three separate occasions, instead of by three psychiatrists.

3. Evaluation by Psychiatrists in Charge of Selection and Treatment: The two psychiatrists who selected the cases and administered the treatment completed a clinical summary on each patient and kept records of their clinical impressions of the patient's condition at the end of 8 and 12 weeks after beginning treatment.

Results of Treatment

Evaluation of the Groups.—A total of 111 patients were selected for the study and were considered at the time of selection to fit the criteria described above. Five of these patients were lost to the project by transfer to another hospital before completion of treatment (three cases), by the refusal of the family to permit treatment (one case), or by the onset of physical illness after selection but before treatment was instituted (one case). There were 106 cases which remained, and which have been in-

TABLE 1.—*Results of Fergus Falls Ratings of Cases on the Acute Ward Which Have Been Rated Two or More Times by the Same Person**

	Im	NC	W		Im	NC	W
A Work	C 11	17	9	G Mood	C 20	12	5
	E 21	10	4		E 13	16	6
B Response to meals	C 10	23	4	H Attention to dress & person	C 14	20	3
	E 16	14	5		E 19	14	2
C Response to other patients	C 16	15	6	I Psychomotor activity	C 21	8	8
	E 20	15	0		E 17	14	4
D Response to PT's and RN's	C 19	15	3	J Speech	C 17	14	6
	E 17	17	1		E 17	16	2
E Response to physicians, etc.	C 10	22	5	K Grooming & toilet behavior	C 4	30	3
	E 14	17	4		E 6	28	1
F Response to treatment	C 11	21	5	L Sleep	C 9	26	2
	E 12	18	5		E 5	29	1

* Im=improvement; NC, no change; W, worsening. C=chlorpromazine group; E, EST group.

cluded in the analysis of the results of treatment. In terms of previous mental illness, the two groups were similar: Of 52 EST cases, 22 had had previous episodes of mental illness, as had 23 of 54 CPZ cases. Thirteen of the EST cases were in the hospital for more than six months after treatment was begun, as compared with four cases in the CPZ group who needed hospital treatment for more than six months. All other patients were out of the hospital before the end of six months.

Statistical Analysis of Ward Personnel and Psychiatric Interviewer Ratings.—One of the instruments used to measure patient improvement was a modification of the Fergus Falls Behavior Rating Sheet. These ratings were made by ward technicians or nurses. On the acute treatment ward there were 37 CPZ cases who were rated at least twice by the same person. There were 35 EST cases of this sort. Each case could be scored as to improvement shown, no change shown, or worsening. Each Fergus Falls Scale was analyzed separately, since we have no basis for treating them additively. The results are shown in Table 1. Of all these scales, only A (Work) exhibits a contrast between the two groups which is significant at the 5% level. Of course, this rating covered only approximately eight weeks of each patient's hospitalization. Perhaps if ratings at the beginning and the end of hospitalization could have been compared, some differences between the groups might have

become apparent, but the patients were usually transferred from the initial ward to another and ward personnel changed. Hence, beginning and ending ratings in almost all cases would have been made by different persons; and, although all ward personnel were given the same instruction, we have no basis for knowing that their standards of judgment are identical, and hence no way of comparing ratings made by different persons. The limited findings from the Fergus Falls Rating Sheet are at least suggestive that the two forms of treatment are essentially equivalent.

Sixteen behavioral factors ascertained in a psychiatric interview were selected for inclusion in the Hickerson Revision of the Goodrich Psychotic Rating Scale. A line for each factor could be checked at any point to indicate the rater's judgment of the amount of that factor apparent. Four points on the line were defined as guideposts. The extreme represented the most pathological aspect of this factor; the other extreme, "normality" in this factor, with two intermediate steps. Thus, by simply measuring the position of the checked point with a ruler, it was apparent whether the patient was judged to have improved or worsened in that factor. For certain factors two-way scales had to be constructed. Thus, for mood, the scale would go from "exhilarated" to "appropriate," and then in the reverse direction to "deeply depressed." These two-way scales were more difficult to analyze

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TABLE 2.—Ratings by Psychiatrists on the Hickerson-Goodrich Scale of Patient Improvement: One-Way Scales *

		W	Im	
A Recent memory	CPZ	11	43	$\chi^2 13.98$
	EST	29	21	
B ₁ Time orientation	CPZ	2	52	$\chi^2 3.21$
	EST	8	42	
B ₂ Place orientation	CPZ	1	53	Exact one-sided P
	EST	7	43	0.023
B ₃ Person orientation	CPZ	1	52	Exact one-sided P
	EST	6	44	0.043
C Intellectual functions	CPZ	6	48	$\chi^2 4.64$
	EST	15	35	
F Looseness of associations	CPZ	5	49	$\chi^2 1.03$
	EST	9	41	
G Affect	CPZ	9	45	$\chi^2 .50$
	EST	5	45	
I Delusions	CPZ	4	50	$\chi^2 3.37$
	EST	11	39	
J Hallucinations	CPZ	2	52	Not significant, by inspection
	EST	4	46	
M Autistic thinking	CPZ	2	52	$\chi^2 3.21$
	EST	8	42	
N Readiness for discharge from hospital	CPZ	0	54	Exact one-sided P
	EST	3	47	0.108

* Im=improvement; W, worsening, CPZ-chlorpromazine group; EST, electroconvulsive therapy group.

than was the case with the one-way scale. The same rater or raters rated each patient at 0, 8, and 12 weeks.

In comparing the two groups of patients, only "improvement" was considered, regardless of the extent. Table 2 presents the results of the comparison of the two groups on each of the subscales from 0 to 12 weeks. All χ^2 values have been corrected for continuity. Of these, A, B₂, and C are clearly significant at the 5% level and B₁, I, and M are near to significance at that level. More refined analysis suggests that B₁ and I do differ significantly at the 5% level but that M does not. It is interesting to observe that in every case except Scale G there is some excess of improvement in the CPZ group as compared with the EST group.

On the two-way scale a problem of analysis was presented, since, for example, a certain patient might be rated at one time as "somewhat overenthusiastic," whereas in a later rating his behavior might have passed through the "normal" area and be rated as "slightly despondent." To try to handle this difficulty, a graphic method was employed,

TABLE 3.—Ratings by Psychiatrists on the Hickerson-Goodrich Scale of Patient Improvement: Two-Way Scales

		a	b	c	d
D Psychomotor activity	CPZ	31	10	5	8 $\chi^2 3.382$
	EST	27	11	1	11 $P > 0.25$
E Speech production	CPZ	31	11	3	9 $\chi^2 1.584$
	EST	25	11	6	8 $P > 0.75$
H Muscular tension	CPZ	39	3	0	11 $\chi^2 3.556$
	EST	35	4	3	8 $P > 0.25$
K Rapport	CPZ	30	11	7	6 $\chi^2 1.801$
	EST	28	11	4	7 $P > 0.75$
L Mood	CPZ	31	12	5	6 $\chi^2 1.30$
	EST	24	14	7	5 $P > 0.75$

where the ratings were plotted. It was thus possible to break the ratings down into four "regions." At any point in region "a" the rating changed to less abnormal. Any point in "b" underwent a mild reversal in the nature of the abnormality. Any point in region "c" suffered a strong reversal, going from a mild abnormality to a severe one of opposite sense. Any point in region "d" became more abnormal in the same sense as the original value. The two groups were compared as to the number of a-, b-, c-, and d-type patients. The results are summarized in Table 3. None of these scales shows significant difference, but, again, looking at "a" (the group which showed certain improvement), there seems to be a tendency to favor the CPZ group.

Measurement of reliability is always, in part, a matter of definition. Table 4 illustrates the method used. For each patient on each scale the distance from "normal"

TABLE 4.—Method Used to Compute Reliability on the Hickerson-Goodrich Scale

	Raters	Weeks		
		0	8	12
(a)	A	30	16	0
	B	24	9	8
	C	17	11	-1
(b)	A	13	4	2
	B	13	4	2
	C	13	4	2
(c)	A	3	2	1
	B	3	2	1
	C	3	2	1

was measured with a ruler. Table 4(a) shows the measured distances for one patient on one scale at 0, 8, and 12 weeks by raters A, B, and C. Table 4(c) shows the measured distance for another patient on the same scale. In calculating reliability, the ruler-measured magnitude of scores was disregarded, keeping only the ranks of the three scores assigned by a rater. Thus, the data in both 4(a) and 4(b) could be represented in rank-order terms by Table 4(c). In the illustrated cases we would say there was "perfect" interrater correlations, using the present methods.

It is a computational fact that where all three raters rated the patient on all three occasions, the average intercorrelation of the ranks is readily obtained from the sums of the ranks of 0, 8, and 12 weeks. Where a protocol is incomplete, the computation is more arduous.

The method described was inapplicable on Scales B₁, B₂, B₃, and J of the Hickerson-Goodrich Scale, because on those scales a large proportion of the subjects were "normal" throughout. Of these, we have an indirect indication of positive reliability in the cases of B₁, B₂, and B₃, since the contrast between the groups was significant, or nearly so, for those scales. If a scale discriminates between groups, then it is measuring something; that is, it has positive reliability.

The average intercorrelations (by ranks) on the other scales are shown in Table 5. In interpreting this Table, it should be noted that the standard error of any figure in a certain column is indicated at the head of the column. The standard error of the two figures in the columns headed "pooled" is approximately 0.085, so that in any row where these two figures average 0.17 or more we have evidence of reliability.

This leads to the conclusion that the evidence in this (small) study is sufficient to show that, except for Scale A, each scale in the Table does measure something. In the case of Scale A we have independent evidence that it measures something from the fact that it emphatically discriminates between the two groups.

Length of Hospitalization.—The actual length of hospitalization (from the date treatment was begun) was calculated for each patient. Of the EST group, which totaled 52 cases, 13 patients were in the hospital over six months. The median time in the hospital for the EST group was 105.5 days. In the CPZ group, of 54 cases, 4 patients remained in the hospital over six months. The median time in the hospital for the CPZ group was 89.5 days. The difference is significant by Wilcoxon's Two-Sample Test at the 1% level of significance.

Side-Effects Associated with Treatment.—The chief side-effects associated with EST

TABLE 5.—Recapitulation of Interrater History Agreement on Hickerson-Goodrich Scale*

Scale	$\sigma=0.118$		EST	$\sigma=0.11$		CPZ	$\sigma=0.129$	
	Complete	Incomplete		Pooled	Complete		Complete	Incomplete
A	-0.017	-0.032		-0.023	-0.025	0.220		0.098
C	0.114	0.227		0.163	0.40	0.163		0.276
D	0.307	0.537		0.440	0.501	0.066		0.270
E	0.209	0.525		0.396	0.471	0.356		0.411
F	0.021	0.421		0.193	0.345	0.59		0.456
G	0.250	0.463		0.315	0.225	0.227		0.226
H	0.372	0.547		0.446	0.158	0.117		0.137
I	0.003	0.644		xx	0.258	0.303		0.281
K	0.194	0.352		0.262	0.346	0.169		0.253
L	0.142	0.580		0.330	-0.046	0.199		0.082
M	0.149	0.708		xx †	0.466	0.352		0.404
N	0.483	0.630		0.546	0.509	0.909		xx

* 12 cases on EST complete; 9 incomplete; 10 cases on CPZ complete; 11 incomplete. Figures are average rank correlations among raters.

† xx means values disagree too strongly to be pooled.

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in this series were the subjective fear of the treatment and the temporary confusion and memory loss. There were no fractures which were clinically diagnosed in those patients receiving EST, and therefore chemical modification of the treatment was not utilized. The period of temporary memory loss and confusion associated with EST is well known to all who have utilized this treatment method. These symptoms had usually subsided by a month after the last treatment. The subjective fear of EST, however, was one effect not easily quantified. In a large state hospital, such as the Agnews State Hospital, it is necessary to give 50 to 100 treatments, at a frequency of three times weekly, on the female acute treatment ward. Those patients who are on EST exhibit considerable anxiety, fear, and tension, and occasionally are physically resistive to their treatment. As the psychiatrist comes into the ward on treatment mornings, there will be a large group of patients waiting, with a large number of reasons why they should not be treated that day.

The most frequent side-effects of chlorpromazine treatment in this group of 54 women receiving an average of 800 mg. daily are tabulated.

No. of Cases

Somnolence, requiring dextroamphetamine modification	18
Parkinsonoid syndrome, requiring benztropine (Cogentin) modification	8
Parkinsonoid syndrome, requiring no chemical modification	7
Skin rash, requiring antihistamine or steroid or both	13
Severe skin rash with facial edema	3
Convulsive seizure	1

There were many cases of transient maculopapular rash of the trunk and extremities, which appeared in the first two weeks of treatment and disappeared spontaneously within a few days without any treatment. Since many of these were probably not noted, we cannot tabulate the number. There were many cases of mild somnolence which did not require dextroamphetamine modification. There were no

cases of known liver damage, jaundice, or leukopenia. All patients on CPZ therapy had base line and weekly white blood cell counts and urine examinations for bile while on treatment. There were a number of episodes of transient orthostatic hypotension during the first few days of treatment, but these were treated by having the patient lie down on her bed. There were three cases of severe generalized maculopapular rash with facial edema. Two of the three patients were taken off chlorpromazine. One of the two patients taken off chlorpromazine exhibited an exfoliative dermatitis and was transferred to the medical ward for treatment. All three patients responded to hydrocortisone therapy. The one patient who had a grand mal seizure was receiving a daily dose of 2,000 mg. at the time of her single seizure. She had no history of prior seizures. The dose was reduced immediately, and there were no subsequent seizures. All patients with Parkinsonoid syndrome showed rapid clearing of their rigidity, mask-like facies, pill-rolling tremor, and shuffling gait when the dose of chlorpromazine was reduced or discontinued. The presence of a Parkinsonoid syndrome was not considered reason for reducing the dose or discontinuing treatment.

Comment

The study was designed to compare, under controlled conditions, the efficacy of EST and chlorpromazine in the treatment of acute schizophrenic and manic reactions. A group of 52 patients on EST and 54 patients on chlorpromazine were similar in that all members of the group were clinically considered to be undergoing an acute schizophrenic or manic reaction before treatment was begun. The treatment methods for the entire group were similar except that one group received EST and the other received chlorpromazine. Thus, it was felt that insofar as possible we had established a controlled situation in which two similar groups received similar treatment programs except for the variable of EST or chlorpromazine, and that we could justifiably draw some conclusions

about the efficacy of chlorpromazine as compared with EST from the evaluation of the results of treatment.

Evaluation of the results of treatment was done by the ward personnel, by psychiatrists who were not in any other way connected with the patients or the study, and by the psychiatrists who were in charge of the treatment program and who carried on the study. There were 37 CPZ cases and 35 EST cases in which the patients were rated at least twice by the same ward personnel. These ratings were done using the Fergus Falls Behavior Rating Sheet. The Fergus Falls ratings were subjected to statistical analysis, and it was found that there was no significant difference between the two groups, using these data.

The ratings done by psychiatrists who were not in any other way connected with the patients or the study utilized the Hickerson Revision of the Goodrich Psychotic Rating Scale, and the patients were rated before treatment, during treatment (8 weeks) and after treatment (12 weeks). The 16 factors of behavior ratings were subjected to statistical analysis, and it was found that there was no significant difference between the two groups, using these data. Thus, by these rating scales, which were completed by the ward personnel and by psychiatrists, the two forms of treatment seemed to produce essentially equivalent degrees of improvement.

In comparing the length of hospitalization for each group, it was found that the median patient in the CPZ group (89.5 days) left the hospital 16 days sooner than the median patient in the EST group (105.5 days). There were 13 patients in the EST group who had to be hospitalized longer than six months, as compared with four patients in the CPZ group who had to be hospitalized more than six months. The CPZ patients were able to leave the hospital sooner than the EST patients, and fewer patients remained in the hospital more than six months when they were treated with chlorpromazine.

We have discussed the side-effects associated with EST and chlorpromazine and noted that there were no significant side-

effects associated with either form of treatment which could not easily be controlled on a state hospital treatment ward by chemical modification.

We should note the considerable subjective fear of EST, which was not present in those patients treated with CPZ. On this basis alone, we feel that there is some advantage in using chlorpromazine, as compared with EST. Since in this group the CPZ patients left the hospital significantly earlier and fewer remained in the hospital for long-term treatment, we also feel that this factor is an additional advantage in using chlorpromazine. It has been noted that the CPZ treatment is a more expensive therapeutic method than EST, but when we note that the CPZ group remained in the hospital fewer days than the EST group, we may suggest that the decreased cost of hospitalizing these patients would be sufficient to pay for the cost of chlorpromazine. Even if cost were no factor, the fear of EST felt by the patients would indicate the desirability of finding some treatment method less frightening to them.

Summary

A group of 106 women on the acute treatment service of Agnews State Hospital were diagnosed as showing acute schizophrenic or manic reactions and were selected to compare the efficacy of chlorpromazine and EST. Of these, 54 patients were treated with chlorpromazine, and 52 were treated with EST. The treatment program was so organized as to make the only variable the EST or the chlorpromazine.

Ratings by psychiatrists not otherwise associated with the patients and ratings by ward personnel showed approximately equal degrees of improvement as measured by the Fergus Falls and Hickerson-Goodrich Scales.

It was found that the CPZ patients were released from the hospital at a median time of 16 days sooner than the EST patients. Thirteen patients in the EST group remained in the hospital more than six months,

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as compared with four patients in the CPZ group.

Side-effects from both types of treatment were found to be not serious and easily controlled. The exception to this statement was the subjective fear of treatment seen in the EST group.

It was felt that chlorpromazine therapy compares favorably with EST in this study as a treatment method for acute schizophrenic and manic reactions.

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A Clinical Comparison Study of the Effects of Reserpine and Placebo on Anxiety

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Within recent years considerable attention has been directed toward the therapeutic effects of reserpine (alkaloid of *Rauwolfia serpentina*) on a large variety of emotional disorders, and many favorable reports have appeared in both medical and lay publications. Noce et al.,^{1,2} Barsa and Kline,³ Kline and Stanley,⁴ and Hollister et al.⁵ were among the first to report on its effects on mentally ill patients. These studies were limited to hospitalized patients who manifested psychotic disorders of varying duration, type, and degree.

More recently, Hare, Seager, and Leitch⁶ reported a study of the effects of reserpine as compared with those of amobarbital and of an inert control substance on 42 neurotic inpatients. These authors concluded that amobarbital produced much improvement in a great majority of their patients, whereas the results with reserpine were no better than those with the placebo. They suggested the need for caution in accepting some of the earlier enthusiastic reports on the efficacy of reserpine.

Davis and Shepherd⁷ reported a comparative study of reserpine and placebo effects on 67 outpatients manifesting chiefly anxiety or depression. They concluded that severely depressed patients did not respond favorably to reserpine. Freis⁸ observed that five hypertensive patients treated with reserpine over a period of several months

Submitted for publication July 24, 1958.

This study was made at the Mental Health Centers of the State of Illinois, 2449 W. Washington Blvd.

Kenneth S. Isaacs, Ph.D., helped in the design of the portion of the experiment involving psychological testing, and Ernest Ni, Ph.D., assisted in the statistical evaluations.

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became depressed. In a similar study, Folksom and May⁹ failed to confirm the impressive claims of the effectiveness of the drug in a number of psychotic disorders.

In critically evaluating the therapeutic efficacy of any new pharmacological agent, it is necessary to take cognizance of the fact that extensive changes can be produced by factors other than the actual pharmacological action of the drug. Drake and Ebaugh¹⁰ directed attention to such considerations as the influence of suggestibility and subjective factors in the evaluation of any new drug, to the difficulty in determining how much change can be attributed to psychotherapy alone and how much to the drug. Wolf and Pinsky¹¹ noted the occurrence of "toxic reactions" following the administration of placebos!

Method

This clinical study of the effects of reserpine was designed to eliminate or control as many variables as possible by the use of a double-blind technique, using each patient as his own control.

The investigation was restricted to patients seen at an outpatient clinic.* Although it would have been desirable to have included all patients who came to the clinic, this was considered unfeasible. Many of the patients, including those who were overtly psychotic or markedly depressed, would have required administration of massive doses of the drug and close supervision, circumstances which are either inadvisable or impossible in an outpatient setting.

The criteria for the selection of patients for this study were the presence of anxiety and/or its manifestations. These were evaluated on the basis of subjective complaints, clinical evaluations, social functioning, productivity as reported by the patients and their relatives, and psychological tests.

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ANXIETY—EFFECTS OF RESERPINE AND PLACEBO

Beginning on a prearranged date, all new patients who contacted the clinic whether by incidental drop-in, telephone contact, or agency referral, and who appeared to meet the criteria for selection were given an appointment to be seen at the study-intake to determine their suitability for the study. In order to minimize the effects of a psychotherapeutic relationship, contact with the patients was as brief as possible, and this was especially so with the psychiatrists. Special forms were designed for the use of each discipline to insure uniformity of procedure in the questioning and examination of each patient.

The patient was first seen by the examining psychiatrist who decided whether the patient would be included in the study on the basis of physical or mental indications. For those patients selected, the physician filled out a check list of relevant data related to the complaints and physical examination. The patient, and relatives when available, then were interviewed separately by a psychiatric social worker, who obtained a selective case history following a specially prepared, specific outline. The patient then was seen by a psychologist who administered a brief battery of psychometric and projective tests. These included the TAT, Seguin Form Board, a number-cancellation test, and a paper-maze and digit-symbol test, to study psychomotor manifestations, stress reactions, and personality characteristics. The patient then returned briefly to the examining psychiatrist, who gave the patient a standard prescription for 22 tablets of medication, with instructions to take one tablet at bedtime each day. An appointment to return in three weeks to see the same examining physician was made. The patient then took the prescription to the clinic pharmacist, who dispensed free either 1.0 mg. of reserpine tablets or identical inert placebo tablets, according to an ABBA order, arranged by and known only to the pharmacist. The pharmacist retained all records of medication until the formal study was concluded and analysis of the data had proceeded to the stage where the information would have no influence on the evaluation of the results.

The selection of a daily dose of 1.0 mg. of reserpine and an administration period of three weeks as being adequate to produce observable pharmacological effects of the drug was based on our previous experience and the work of Freis and Ari¹² and Hare and associates.⁶

At the end of three weeks the patient was re-examined in the same order, using the same check lists, with specific inquiry as to possible changes in his condition. The patient was again seen briefly by the physician, was handed a prescription for 22 tablets with instructions as before, and was given another appointment for three weeks. The prescription was filled by the pharmacist, who

dispensed tablets alternate to those he had given out previously. At the end of the second three-week period, the patient was seen for the third time and was examined in the manner already described.

Results and Observations

Of 71 patients who were selected as suitable for the study, 42 completed the six-week observation period. These latter included 27 men and 15 women, with an age range of from 19 to 44.

Analysis of all the data accumulated in the study revealed that the patients observed could be divided into four groups according to their responses in both three-week periods (phases) of observation (Table 1).

- Group A: 13 patients who responded favorably in both phases
- Group B: 13 patients who showed no change in either phase
- Group C: 10 patients who improved only in the second phase
- Group D: 8 patients who improved only in the first phase

Since it is evident that there were responses and lack of responses in both phases, efforts were made to delineate factors which could account for the differences. It became apparent that such factors as age, sex, family history, and previous therapy had no significance as determinants for comparison. There was no correlation between diagnostic categories and occurrence of either negative or positive response. As in Feldman's¹³ observation, it was noticeable that the objectivity of these observations was influenced by the observer's psychiatric orientation and subjective attitude toward the drug under study. A less variable area was the periodic observation of the physiological concomitants of anxiety, including blood pressure, pulse rate, sweating, and tremors. However, there was frequently no relationship between the physiological changes and the subjective findings. The least variable and, therefore, most valuable area of observation was the patient's own description of his symptoms and the subjective assessment of his over-all situation during the periods of observation. This is in agreement with

TABLE 1.—*Complaints in Four Groups Based on Responses in Phases of Observation*

		Complaints				Complaints							
Patient No.	Group A Improved in Both Phases	Diagnosis	Psychoneurotic	Affective	Somatic	Interpersonal	Patient No.	Group B Improved in Neither Phase	Diagnosis	Psychoneurotic	Affective	Somatic	Interpersonal
1	Obsessive-compulsive c somatization			x			1	Schizoid personality		x	x	x	x
2	Borderline		x	x	x		2	Inadequate personality		x	x	x	x
3	Emotional instability		x		x		3	Passive-aggres., aggres. type		x		x	x
4	Anxiety reaction		x		x		4	Hysterical pattern dist.		x			x
5	Anxiety reaction		x	x	x		5	Chronic schizophrenia			x		
6	Compulsive personality		x		x		6	Passive-aggres., passive		x	x		x
7	Personality pattern		x		x		7	Inadequate personality		x			x
8	Hysterical character			x	x		8	Inadequate personality		x		x	
9	Compulsive personality		x		x		9	Passive-aggres. personality		x		x	
10	Chronic schizophrenia		x				10	Hysterical personality		x	x	x	x
11	Personality pattern		x		x		11	Anxiety reaction		x	x	x	x
12	Hysterical		x	x	x					—	—	—	—
13	Hysterical pattern in disturbance			x	x				Totals.....	10	6	7	8
	Totals.....		10	2	10	6							
Group C													
Improved in Second Phase Only						Group D							
1	Compulsive personality	x		x		1	Compulsive personality		x	x	x	x	
2	Personality pattern dist.	x	x	x	x	2	Passive-aggres. personality		x		x		
3	Personality pattern dist.	x				3	Chronic schizophrenia			x			
4	Personality trait dist.	x		x		4	Chronic schizophrenia		x		x	x	
5	Anxiety reaction	x		x		5	Personality pattern dist.		x		x	x	
6	Passive-aggres. c somatization	x		x	x	6	Chronic schizophrenia		x	x	x		
7	Schizoid personality	x	x			7	Anxiety reaction		x				
8	Adult situational reaction	x			x	8	Passive-aggres. personality					x	
9	Schizoid personality	x		x					Totals.....	—	—	—	—
10	Inadequate personality	x		x	x					5	3	3	5
	Totals.....		10	2	6	6							

Hare et al.⁶ who felt that "the effects of drug treatment in an anxiety state are possibly best assessed by the self-observation, under controlled conditions, of a co-operative and intelligent patient."

A comprehensive survey of the character of the complaints of all the patients in the study demonstrated that these symptoms fell into four groups.

Affective: Here the complaints centered around disturbances of affect. These included uncontrollable anger, hostile outbursts, loss of temper and feelings of moodiness, sadness, crying, and varying degrees of depression.

Somatic: The complaints centered around disturbances listed in the diagnostic manual of the American Psychiatric Association as "physiologic, autonomic and visceral disorders." The symptoms in the group involved the cardiovascular, musculoskeletal, nervous, respiratory, and gastrointestinal systems.

Interpersonal: The complaints pertained to disturbances in the relationships of the patient with other people, such as spouse, children, siblings, parents, employers, fellow employees, or employees.

Psychoneurotic: The complaints were those in which anxiety was the primary subjective manifestation. The anxiety was described either as free-floating (feelings of tension) or as components of phobias, obsessions, or compulsions.

A breakdown of these complaints into the four groups described above is shown in Table 1. The relationship between these symptomatic determinants and the occurrence of improvement is illustrated in Table 2. Of the total of 42 patients observed, 31 improved in either or both phases of the study, and 11 improved in neither. Of the 31 who showed improvement, only 7 (23%) manifested affective complaints, whereas of the 11 who showed no improve-

ANXIETY—EFFECTS OF RESERPINE AND PLACEBO

TABLE 2.—Relation of Predominant Complaints to Occurrence of Improvement

	Totals	Psycho-neurotic	Affective	Somatic	Interpersonal
Improved in either or both phases	31	25 (81%)	7 (23%)	19 (61%)	17 (55%)
Unimproved in either phase	11	10 (91%)	6 (55%)	7 (64%)	8 (73%)

ment there were 6 (55%) with affective complaints.

The relationship of the numbers of patients improved and unimproved to the tablet administered and the phase in which it was administered are shown in Tables 3A and 3B. It will be observed from Table 3 that during the first phase more patients responded favorably to placebo than to reserpine. This seems to indicate that the element of suggestibility has a considerable influence on the character and degree of response. Our findings agree with those of Wolf and Pinsky,¹¹ who compared the effects of mephenesin and placebos on anxiety and its manifestations and found almost the same amount of improvement or lack of it regardless of which the patient was taking. However, these authors attributed the positive effects observed when placebos were administered to the physiological and toxic effects of placebos, whereas we believe these effects to be the results of the suggestion which is implicit in the giving of pills

to a patient who seeks and expects help. In the experiment of Wolf and Pinsky¹¹ there was, in addition, verbal suggestion. "At the beginning each patient was told that he was being given a medicine to allay his tension and anxiety and to relieve muscle pains, if he had them."

In the second three-week period of observation more patients responded favorably to reserpine than to placebo. It might be assumed that the effects of suggestion become quickly apparent and subside rapidly, and that then the effectiveness of the drug becomes more evident. However, this assumption was not borne out when the data were subjected to a statistical analysis, which revealed that there was no significant difference in the proportion of patients improved between those who took reserpine and those who took placebo. The difference apparent here was a chance difference due to sampling variation.

Clinical and Psychological Observations of Characters of Patients in Various Groups

Patients Who Improved in Both Phases (Group A).—Many of the patients in this group became disturbed as a result of some external demand which tended to disturb their emotional equilibrium. Most frequent in the case of men was the wife's pregnancy. The anamnesis revealed a similar reaction to the wife's previous pregnancies. Unconsciously, such a situation had deep determinants, but on a more superficial level it meant the assumption of added responsibility.

The cause-and-effect relationship was demonstrated especially well in one of our patients. During the initial examination the patient appeared very anxious and agitated. On exploration it became apparent that he had established a passive, dependent relationship with his wife, who was about to give up her employment as she was approaching her fifth month of pregnancy. After three weeks, during which he was taking reserpine, the patient appeared markedly improved. Inquiry revealed that during the

TABLE 3.—Relation of Improvement to Phase in Which Tablet Was Administered.

Medication	Total Patients	No. Unimproved	No. Improved	Per Cent Improved
First Phase				
Reserpine	21	12	9	43
Placebo	21	9	12	57
Totals	42	21	21	50
Second Phase				
Reserpine	21	7	14	67
Placebo	21	12	9	43
Totals	42	19	23	55

interval his wife had had a miscarriage. During the following three weeks he was on placebo, and the improvement observed continued. This case points up the question as to what the therapeutic agent was in the improvement of this patient. Was it the medication or the alteration of an external pressure which permitted reestablishment of patient's previous emotional equilibrium?

Another observable feature in these patients was the need for passive dependent gratification. Any event (as illustrated above) which deprived the patient or threatened him with the loss of such gratifications led to symptom formation. Some patients in the group stated that they felt better as a result of the knowledge that something was being done or would be done for them. In a few the improvement was very striking regardless of the composition of the pill they were taking, and it was obvious that they had a tremendous need to deny the real, underlying factors in their disorders. The pills were used in the service of a flight into health.

Psychologically, the patients in this group seemed to be overwhelmed by responsibilities and demands which were put upon them. They wanted to regress to an earlier period of life in order to be able to receive care from others. This tendency was apparent in those who manifested marked ego weakness. Several patients were of low average intelligence. A few displayed histrionic features in their character formations; a number of them revealed active strivings to counteract dependent needs; several others contemplated the adoption of such strivings but hesitated because of unwillingness to give up the dependent needs. On an unconscious level, they manifested dissatisfaction with the mother and anger because of her failure to fulfill their needs. These are strongly oral dependent in character, such as the need for attention, care, and closeness.

Patients Who Improved in Neither Phase (Group B).—The most striking clinical manifestations were in the affective sphere. In four patients the presenting symptom

was that of explosive, aggressive affect. They were volatile, irritable, and grouchy, hollered, and were generally argumentative with everyone. Also in this group were six patients who were prone to depression; and as contact with them was continued, this affect became intensified gradually. There did not appear to be any close correlation between the kind of pill which the patients were taking and the developing depression, since it developed in three patients while on reserpine and in the remaining three while on placebo. Another observable factor was that of secondary gain from illness, financial or to avoid an undesirable external situation. Three of the patients were in the process of applying for a pension. Another used his illness to avoid marriage.

Psychologically, patients in this group fell into two subgroups. A predominant number (Subgroup B₁) revealed conflict with parental figures. They were moralistic and, therefore, prone to marked feelings of guilt. Thus, when they were confronted by competitive feelings with parental figures, they reacted with depression. This experience was followed by an inhibition of mature strivings and a defensive acceptance of a passive-dependent position. The second subgroup (B₂) consisted of four patients who appeared generally ineffectual, were of dull normal intelligence, possessed few resources to deal with their problems, or had little energy to invest in meaningful relationships.

Patients Who Improved Only in the Second Phase (Group C).—In many respects the patients in this group were similar to those in Group A. Many of them sought psychiatric help as a result of external pressures. When these pressures subsided, there was concomitant improvement regardless of the nature of the medication dispensed. Some of the patients felt relieved, as they expressed it, by the knowledge and expectation that they had come to a setting where they would be protected and cared for.

Psychologically, the patients in this group were similar to those in Subgroup B₁. They manifested marked problems with authority,

but, unlike those in Subgroup B₁, patients in this group were fearful of being punished; or, when confronted by such figures, they were overwhelmed by a mobilization of marked sadistic feelings, which they feared they might not be able to control. The defense was to regress and abandon mature strivings, to function with extreme caution, or, finally, to project their sadistic impulses onto others.

Patients Who Improved Only in the First Phase (Group D).—These patients were closely related to those in Group B. During the period of contact the over-all picture became more disturbed, with manifestation of severe depression and feelings of estrangement and unreality, with bizarre phobias, delusions, or hallucinations. It is interesting that in this small group three of the patients were on reserpine at the time that the more disturbing symptoms became observable.

Psychologically, the patients in this group were those generally considered as borderline. They were limited in their adaptive resources, negative, and hostile. They were emotionally labile and prone to marked depression and feelings of hopelessness, especially when overwhelmed by demands that were made upon them. They were emotionally impoverished, lonely, isolated, and constricted in all their thoughts and feelings. Several were overtly psychotic, appeared disorganized, and were given to perseveration and distractability.

Summary and Conclusions

Some of the literature on the effects of reserpine is briefly reviewed.

Forty-two clinic outpatients complaining of anxiety and its manifestations were studied to compare the effects of orally administered reserpine and an identical placebo, using a double-blind technique. Each patient was observed through two three-week phases.

Patients were classified under four groups according to their treatment response. Of the total of 42 observed, 31 improved in

either or both phases, and 11 improved in neither. Of the 31 who improved, 13 improved in both phases; 8 improved during the first phase only, during which 4 were on placebo and 4 on reserpine medication, and 10 improved during the second phase only, during which 4 were on placebo and 6 on reserpine medication.

There was no significant statistical difference in proportion of patients improved between those who took reserpine and those who took placebo.

Predominant complaints were classified under four categories: affective, somatic, interpersonal, and psychoneurotic. Patients who showed predominantly affective complaints tended to show the least response to either tablet.

Many patients who improved demonstrated strong passive-dependent needs and felt better as a result of knowing that something was being done for them and given to them.

There was more improvement in the subjective than in the objective manifestation of anxiety.

Much of the improvement is attributable to the element of suggestion. Though attempts were made to keep this factor to a minimum, the suggestion implicit in the giving of medication to a patient who comes seeking help cannot be eliminated.

Often situational changes occur which result in reduction of environmental pressures and consequent improvement, for which the drug may erroneously be given credit.

A clinical and psychological analysis of patients grouped according to treatment was made.

Caution is indicated in evaluating the therapeutic effects of any drug on the manifestations of anxiety because of the fact that extensive changes can be produced by factors other than the actual pharmacological action of the drug.

It is speculated that the same conclusions would have been apparent had any other

tranquilizing drug been substituted for reserpine in our experiment.

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Status and Work Satisfaction of Psychiatrists

A Comparative Study of Psychiatrists in State Employ and Private Practice

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This summary report on psychiatrists is based on an investigation of status and job satisfaction in five mental health professions. One of the implicit intentions of the study was to help explain difficulties in securing and retaining adequate numbers of well-trained personnel in state schools and mental hospitals. The need for such research is indicated in a report by the National Association for Mental Health listing shortages of personnel in mental health organizations.

We thought that low status of state mental hospital positions might deter prospective employees and that low work satisfaction might influence employee turnover. We therefore predicted that (a) job satisfaction and status in general would be directly related, (b) state institutional positions would be perceived universally as having lower status than nonstate institutional positions, and (c) the job satisfaction of state institutional personnel would be lower than that of nonstate institutional personnel. The present report is confined to the results of investigation of these hypotheses in groups of psychiatrists.

In this short paper, details of the method used can only be given in outline. The data are based on standardized individual interviews with 578 persons in Ohio representing 468 professionals and 110 laymen, the latter divided into upper- and lower-middle-class samples. Of the professionals, 428 repre-

sented five different mental health professions: psychiatry, psychology, social work, teaching, and nursing, each group divided into 40 state-employed and 40 nonstate-employed plus a group of 28 residents in psychiatry. The state employees were selected from 6 different state hospitals and schools; the nonstate professionals came from 27 clinics, agencies, general hospitals, and public schools and from private practice. In addition, there were 40 physicians from nonpsychiatric private practice.

During the interviews, each person was asked to place a set of professional titles according to their status and prestige, using various reference groups. All of the ratings were obtained by means of a new method developed by us and referred to as the magnetic-board rating technique.¹ The 22 professions rated included the 10 professional groups comprising the study sample and 12 additional titles, extending from Supreme Court Justice through various medical specialties down to hospital attendant. The subjects were requested to rate these professions as the general public would rate them. Each professional was then asked to place the magnetic label where he thought the mental health profession as a whole would rate his, where they thought it should be, and then where he thought each of the other mental health professions in the same employment setting would place his. Finally, he was asked to rate these same professions as to where he thought they deserved to be.

The subjects completed a brief 21-item questionnaire, covering such points as income, age, training, publications, and so on, which had previously been assigned weights obtained from pooled ratings of independent

Submitted for publication July 17, 1958.

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judges, so that objective status scores could be secured.

Using the same magnetic-board method, the professionals were requested to assign ratings to the importance of eight factors of job satisfaction, including intellectual stimulation, pay, status and prestige, regular work hours, security, freedom, patient's respect, and type of patient. They were then asked to repeat these ratings according to the degree to which each was supplied them at their work. Finally, to obtain measures of work satisfaction, a scale consisting of five Likert-type items was administered.

The data pertaining to the reliability of the rating and scaling instruments used in this report have been discussed elsewhere.² The retest reliabilities for the magnetic board were 0.987 (means) and 0.815 (individual scores). The job satisfaction scale had a 0.801 split-half reliability. Some of the more theoretical aspects have already been published,³⁻⁵ and some of the findings in regard to certain of the professions are in press.^{6,8} All that will be presented in this report are some of the highlights of the findings regarding the psychiatrists.

It was quite clear from the ratings assigned by both groups of the lay public, that psychiatrists, as a whole, had the lowest status and prestige of all types of physicians. Starting at the top with the surgeon, obstetrician, and general practitioner, the hierarchy descended to the psychiatrists. Both upper- and lower-middle-class groups rated the institutional psychiatrist lowest, even lower than that "low man on the totem pole," the public health physician. Both groups placed the psychologist on the faculty of the university above the institutional psychiatrist. However, the psychiatrist in private practice was not too far above the rank given the institutional man. Neurologists and child psychiatrists were rated somewhat higher than psychoanalysts, who, on the whole, were ranked fairly similarly to the men in private practice. It is interesting to note that, except for nurses and teachers, both groups of psychiatrists under investigation had the greatest amount of

variability in ratings assigned them of all the professions, indicating a good deal of doubt as to where they should be placed. In view of some of the extremely low placements, considerable hostility to the discipline was also indicated.

The state-employed institutional psychiatrist expects and universally receives less status and prestige from all lay and professional groups than does the private-practicing psychiatrist. Psychiatrists in state employ have a lower general feeling of work satisfaction and also believe that their co-workers are dissatisfied. The psychiatrist in private practice is much more satisfied with his work than he believes other professionals or his co-workers to be. Despite these ratings, both groups of psychiatrists do not differ significantly in their feelings of accomplishment.

While the objective status of the private practicing psychiatrist is somewhat higher than that of the institutional psychiatrist, it is not significantly so.

The factors going into the importance of job satisfaction are rated somewhat differently for the two different groups of psychiatrists. The institutional men rate intellectual stimulation as most important, followed by freedom and patient respect. The men in private practice rate freedom first, followed by intellectual stimulation and type of patient. Both groups rank regular hours as last in importance. The institutional group of psychiatrists differ significantly in the higher importance they attach to intellectual stimulation, security, and regular work hours. Pay, as one of the factors in work satisfaction, is rated higher among the institutional psychiatrists, but barely misses being statistically significant at the 5% level.

The institutional psychiatrists indicated that of the eight factors of job satisfaction, their supply of security was highest, followed by intellectual stimulation and patient respect. The lowest supply of these factors was in type of patient, followed by status and prestige. On the other hand, the men in private practice stated that the factor in

STATUS AND WORK SATISFACTION

greatest supply was freedom, followed by intellectual stimulation. In lowest supply were regular hours and type of patient. The institutional psychiatrists differed significantly in their expressions of supply from the private-practicing man in stating that they had oversupplies of regular hours and security.

By subtracting ratings of importance of factors of job satisfaction from expressions of supply, an indication of sufficiency of the factors under consideration could be secured, and, as might be expected, the institutional psychiatrists gave regular hours and security as being present in greatest sufficiency, with intellectual stimulation and freedom most insufficient. The psychiatrists in private practice gave patient respect and security as the factors in greatest sufficiency, with freedom and intellectual stimulation as lowest, those in private practice rating the latter very much the same as did the institutional men. The one factor which showed statistically significant difference in the two groups was that of patient respect, the institutional men being lower as far as sufficiency of this variable was concerned.

The private-practicing psychiatrist is much more realistic as to where others would place him. He actually underestimates the status that some professional groups, such as the psychologists and social workers, would accord him. The institutional psychiatrist, on the other hand, displays the typical behavior demonstrated by all the other professional groups in tending to overestimate the status that others would assign him. However, the man in state employ tends to think that the psychiatrist in private practice has more status in the eye of the general public than he actually has. The psychiatrist in private practice concurs in this, thinking that the institutional man is given less status by the general public than he is given in reality. Despite his actual and expected lower status, the institutional man aspires to a higher status than does the man in private practice, indicating that status and prestige are somewhat more important to him. However,

this difference is not statistically significant. Also, it is interesting to note that both groups think that each should be accorded higher status than the other.

There are a sizable number of additional findings and correlations which could be itemized and discussed. For instance, in both groups of psychiatrists, the higher the job satisfaction, the higher the status expected from the general public, and also the higher the aspired status. However, only the institutional psychiatrist has a significant positive correlation between job satisfaction and the rating he expects from his colleague in private practice. It is impossible at this time to present other similar findings.

The implication of each of the above findings deserves to be discussed individually and in combination, an impossible task under the circumstances. However, broadly speaking, the obviously low status and prestige accorded psychiatry should be of great concern to us. In an area where the patient's opinion of his therapist frequently is one of the important variables in the efficacy of his therapy, it would seem essential that considerable effort be exerted toward raising status. Among the obvious measures, the raising of the scientific and clinical levels of our work seems imperative. This is especially important in view of the marked emphasis psychiatrists themselves place upon intellectual stimulation and freedom in their work, which they also indicate to be insufficient in supply, particularly among the men in institutional work. These are inextricably interwoven with the variable of patient respect, which is, again, in turn, tied up with the generally low status of the psychiatrist.

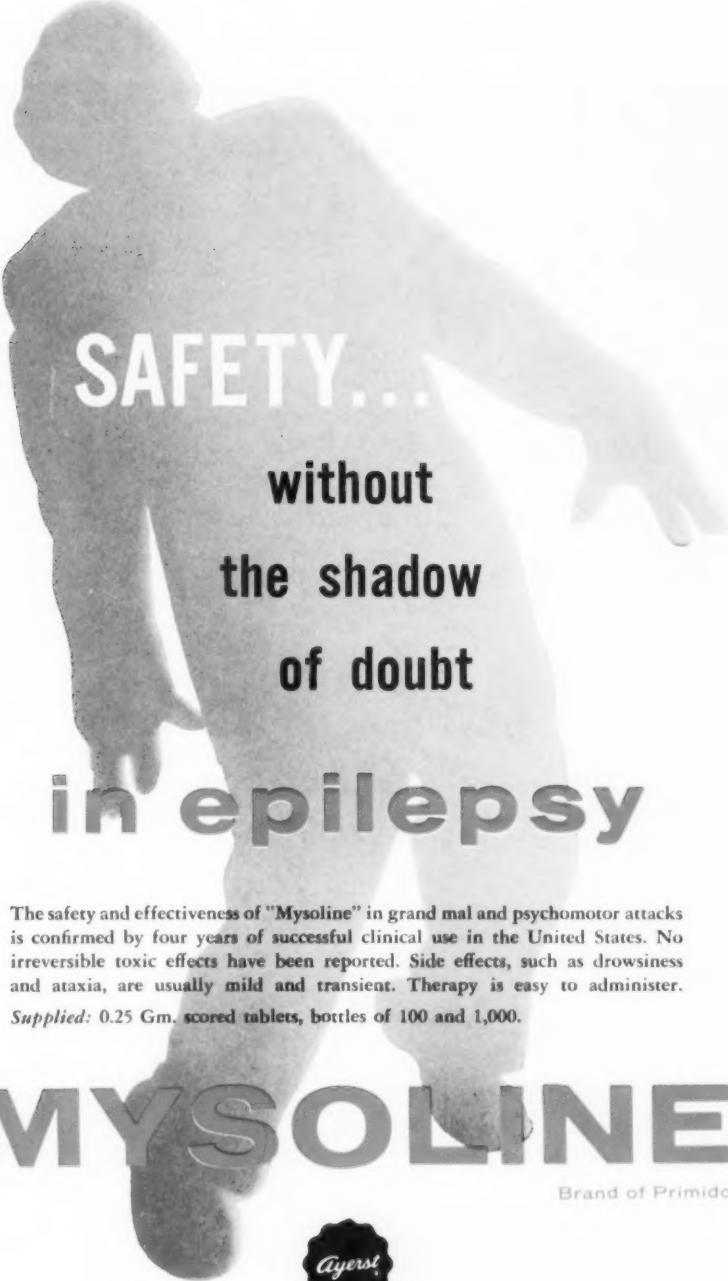
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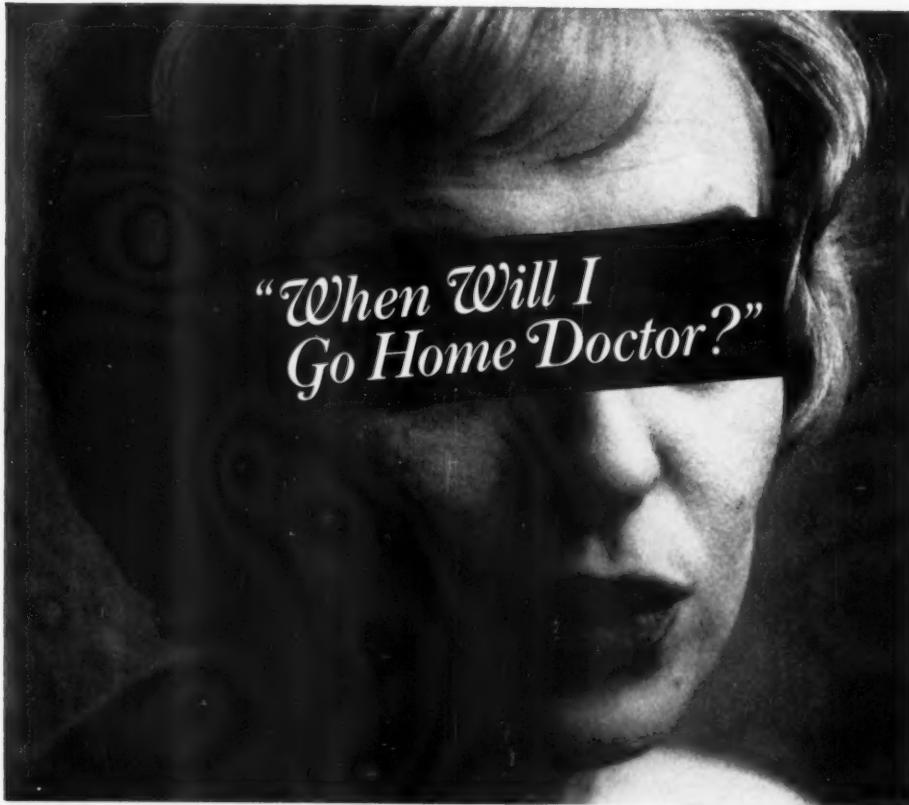
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